Textbook of Pancreatic Cancer

Principles and Practice of Surgical Oncology

Kjetil Søreide
Stefan Stättner
Editors

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Springer

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My heartfelt gratitude and thanks go to my wife Annbjørg and our four boys Jonas, Erling, Tobias, and Daniel for keeping me grounded and for their enduring support and love.

Kjetil

Thanks to my dearest ones for their patience and love: Alexandra, Tobias, Lukas, and Felix—a man is nothing without his family.

Stefan

Foreword

I am delighted to write a foreword for the *Textbook of Pancreatic Cancer: Principles and Practice of Surgical Oncology*.

The field of pancreatic surgical oncology has undergone a resurgence in recent years with the improvements in peri-operative care, advances in operative techniques, coupled with improved understanding of the biology of pancreatic cancer. Professors Søreide and Stättner are to be acknowledged for bringing many of the leading experts in the field from throughout the world to produce a contemporary textbook dealing with the various aspects of pancreatic surgical oncology.

The text is comprehensive, covering the whole spectrum of pancreatic cancer from epidemiology, anatomy of the pancreas, disease burden, biology, diagnosis and staging, therapeutic options, surgical techniques, perioperative care, outcomes, and palliative care. The topics are dealt with in a clear and concise manner. The information presented is up-to-date and useful for both the novice and experienced practitioners.

Addressing the needs of the trainee for a comprehensive textbook on pancreatic cancer in preparation for specialty board examinations, as well as being a suitable reference text for established surgeons who are interested in pancreatic surgical oncology is a difficult assignment. However, I believe that the editors have succeed in this task.

Unlike other texts that deal solely with pathophysiology, this book in addition highlights many of the other controversial issues that are involved in the delivery of pancreatic cancer care such as training, measurement of quality, regionalization, and influences of oncopolitics. This adds to the overall value of the textbook.

Again, the editors are to be congratulated for bringing to fruition this valuable addition to the surgical literature.

Kevin C. Conlon,
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Foreword from ESSO

A foreword usually tells the readers why they should read a book, and I will support my motivations with two arguments.

The first one is based on the quality of the authors: Kjetil Søreide, Professor of Surgery at Stavanger University Hospital, Norway, the youngest person ever to be appointed to a Norwegian surgical chair, and Stefan Stättner, Clinical Lead for Surgical HPB Oncology and in charge of research in this field at the Medical University of Innsbruck, Austria. Both are young and enthusiastic surgeons and researchers, an active and valuable part of the European Society of Surgical Oncology Education and Training Committee.

The second motivation stands in the fact that this book summarizes the actual developments of modern science and technologies which are enabling basic researchers, pancreatologists, gastroenterologists, and pancreatic surgeons to better understand perhaps the least understood of human organs—the pancreas.

Pancreatic cancer is associated with a very poor prognosis, highlighted by the close parallel between disease incidence and mortality. Tumor biology of pancreatic cancer contributes to early recurrence and metastasis, and resistance to chemotherapy and radiotherapy.

A multidisciplinary approach to pancreatic malignancies is considered as essential to provide the best outcomes of patient care. In the last years, there have been considerable advances in the surgical management of pancreatic malignancies. Many of these relate to related specialties (radiology, oncology, gastroenterology, and anesthesia) and also directly to surgery.

Over the past several years, the pool of potentially resectable patients has increased; the use of preoperative therapies has improved the number of patients undergoing margin negative resections. With these changes, and the evolution of chemotherapy and chemoradiation protocols, there is now a growing need to identify predictors of treatment response that move beyond merely documenting changes in tumor size.

The combined efforts of many expert contributors have resulted in a comprehensive broad-ranging textbook concerning the world of pancreatic cancer.

This book does well to bring into sharp focus not only the various pros and cons of technical aspects of pancreatic resections. The improvement in outcomes due to multidisciplinary care and emphasis on finer perioperative aspects such as nutrition and enhanced recovery after surgery further adds to the excitement where the future is only expected to be brighter than ever before.

As Chair of the ESSO Education and Training Committee, I am sure that this work is an exciting and valuable resource, sufficiently comprehensive to cover the broad spectrum of pancreatic cancer for specialists and for candidates coming to UEMS Surgical Oncology examinations.

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Foreword from the President of IHPBA

Pancreatic cancer remains a very challenging disease to treat. The outcomes remain poor, but many technical aspects have improved, and over the last decade, there has been a significant growth in our understanding of the biology, investigations, and treatment of this disease. New approaches including surgical techniques, adjuvant therapies and technologies, and systemic therapies either preoperatively or postoperatively are part of the everyday armamentarium that has evolved. The approach to premalignant conditions will result in an increase in the number of operations performed for this condition.

Unfortunately, there remains a lack of high-level evidence for many of the treatment options, and clinicians still have to rely on good clinical judgment. We are confident that the future will advance our ability to treat this condition. This textbook reflects many of the new innovations and the scientific progress that forms the basis for our future clinical decision-making.

Training the next generation of pancreatic surgeons requires that as best as possible we provide guidance and understanding of the disease and its management. This textbook, through bringing together this remarkable group of experts with an enormous understanding of the disease and huge experience in treating pancreatic cancer, will make a significant contribution to the development of the next generation of pancreatic surgeons and oncologists. Some of the finest clinician scientists and surgeons who have contributed to the current evidence-based understanding of pancreatic cancer from the European pancreatic medicine community have contributed their knowledge and expertise to the content of this textbook. The topics in this textbook cover a wide range of issues relevant to both the general pancreatic surgical community and oncologists but especially for the young trainees developing their own experience and understanding in the management of patients with pancreatic cancer.

The editors have produced a resource that will enhance many of the educational activities of the EAHPBA and the IHPBA and our commitment to education and training. Their significant contribution to this objective is welcomed and appreciated.

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Foreword from the President of the AHPBA

Pancreatic cancer is a leading cause of cancer-related mortality worldwide with an estimated 5-year survival rate of roughly 30% following curative-intent resection and less than 10% for patients with unresectable disease. Optimal treatment for all stages of pancreatic cancer requires a multidisciplinary approach involving specialists such as medical oncologists, surgical oncologists, gastroenterologists, and radiation oncologists among others. In particular, most patients with pancreatic cancer are now cared for using some combination of surgery, chemotherapy, and/or radiation therapy. As such, multidisciplinary care has become increasingly more prevalent in the management of patients with pancreatic cancer. As such, it is critical for surgeons to have a firm grasp on the emerging knowledge regarding the diagnostic and treatment options for patients with pancreatic cancer. In light of this need, Kjetil Søreide and Stefan Stättner have edited a definitive textbook that covers the principles and practice of surgical oncology related to pancreatic cancer. Professors Søreide and Stättner are recognized experts in the field of hepatopancreatic surgery with international expertise on the topic of pancreatic cancer, surgical approaches to the pancreas, as well as the molecular biology of pancreatic cancer.

This book covers a number of important topics including the work-up, as well as medical and surgical management of patients with pancreatic cancer. In particular, an array of expert authors covers a wide range of clinically relevant topics such as pancreatic disease burden, education, training, quality of care, as well as diagnosis, imaging, and staging of pancreatic cancer. I want to commend Professors Søreide and Stättner for enlisting the help of an amazing group of authors who are leaders in the field of pancreatic cancer. As you will witness yourself, the authors do an expert job in highlighting the important and relevant aspects of caring for patients with pancreatic adenocarcinoma. The knowledge contained in this important book will well serve surgeons and other healthcare providers who care for patients with pancreatic tumors. I would like to thank and congratulate Professors Søreide and

Stättner and all the contributing authors for an excellent resource on the principles and practices around pancreatic cancer.

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Preface

It is with great pleasure and immense pride we see this book come to fruition. The inception of this started by means of filling a void of learning material for young surgeons wanting to complete the fellowship exams in surgical oncology and hepatobiliary and pancreatic surgery. As members of the Education and Training Committee in the European Society for Surgical Oncology (ESSO) and also for the European-African Hepatobiliary Pancreatic Association (EAHPBA), we saw a need for a core curriculum that would cover essential themes within pancreatic cancer as we know it. Inspired by the initial ESSO endorsement of the project, we are thrilled to see the keen support also from the HPB societies for the final product.

While not encyclopedic in format, we hope the comprehensive nature of the content will reach a wide audience of clinicians and researchers from several disciplines. Clearly, the content has been tailored with the student, fellow, and practicing surgical oncologist in mind, but the themes covered reaches well beyond the basic clinical content needed for the day-to-day clinical practice. We have included topics that are emerging in the way we understand pancreatic cancer (e.g., the microbiome and molecular biology) and have chapters that address emerging fields of testing, diagnosing, or treating the disease. We envision that novel discoveries will allow for future updated editions of the book, to hopefully document a steady progress in understanding and management of this often-dreaded disease. We hope the comprehensive content may serve as an introduction to the budding student of pancreatic cancer, be a valuable reference to the astute clinician and surgeon oncologist at work, and serve as a comprehensive study tool to fellows preparing for board exams in general surgery, surgical oncology, or hepatobiliary and pancreatic surgery. We also hope that the content may inspire surgeons and those in other disciplines to pursue new knowledge and invest time and effort in trials and basic science to improve our understanding of pancreatic cancer.

As editors, we would like to thank all the authors for their hard work and commitment to the content. This book simply could not have been done without the dedication and expertise provided by each individual and group of experts to each chapter. We are thrilled to see the multidisciplinary, international set of authors covering most corners of the world and represented by most institutions and

departments dedicated to the research and management of pancreatic cancer. We are very proud to have so many women leaders in the field contribute as either coauthors or senior authors of chapters throughout the book. While we have strived to ensure diversity in this multi-authored text, we know we can only do better and express our sincere apologies to any or those who were unintentionally left out from contributing to this edition of the book. Importantly, we appreciate the importance of inclusion, diversity, and the perspective of global health. For any inadvertent errors or missed points we apologize. For novel suggestions or any other feedback, we are more than happy to be contacted—we can only learn and improve by engaging!

We would also like to thank the publishers for their hard work and commitment to deadlines and getting the final versions into production.

The reason for creating this book lies in the hope of improving care and outcomes for patients with pancreatic cancer. It is only appropriate to dedicate this book to the current and future patients who suffer from pancreatic cancer in the hopes that we will see true cure from this disease, to the students of this complex disease who invest time and efforts towards improved knowledge, and to the clinicians and researchers who work towards improved management of pancreatic cancer through basic and translational research, clinical trials, and their day-to-day practice.

Finally, we would like to thank our families who endured the several hours, long days, and many weekends spent by us editing the book on top of a busy clinical schedule.

Stavanger, Norway — Kjetil Søreide
Innsbruck, Austria — Stefan Stättner

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Part V Diagnosis, Imaging and Staging

Part VI Perioperative Care

Part X Palliation and End of Life Issues

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Part I
Pancreatic Cancer Disease Burden

Chapter 1
Risk Factors for Pancreatic Cancer

Oskar Franklin and Malin Sund

Take Home Messages
- Modifiable risk factors for pancreatic cancer are similar to many other cancer forms and cardiovascular diseases.
- Tobacco smoking contributes to the highest attributable fraction of pancreatic cancer risk due to its high prevalence in the general population.
- Chronic pancreatitis is associated with a high risk of developing pancreatic cancer, but the prevalence is low.

Pearls and Pitfalls
- Pancreatitis is associated with the risk of pancreatic cancer, but can also be a manifestation of the disease. Pancreatic cancer should be considered when determining pancreatitis etiology.
- Common risk factors for pancreatic cancer cannot be used to select patients for screening/surveillance.

Future Perspectives
- Increasing genome-wide data resources can be integrated in epidemiological studies to draw more rigorous conclusions about risk factor causality. Such studies could also highlight direct risk associations with genomic variants.

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- The microbiome is increasingly appreciated as a contributor to health and disease, and future studies will determine the contribution of the microbiome in pancreatic cancer pathogenesis and how it relates to pancreatic cancer risk.
- Improvements in defining risk factors can aid in defining high-risk populations. If biomarkers for early detection and more robust imaging techniques evolve it might allow for screening for pancreatic cancer in the future.

1.1 Introduction

Risk factors are variables that are associated with an increased risk of developing the disease of interest. This is generally investigated through observational studies, including case–control and cohort studies. More robust evidence comes from pooled analysis of several studies or a meta-analysis. This chapter focuses on risk factors that have support from meta-analyses and pooled analyses. Risk associations where the evidence is weak has generally been left out in the chapter. Importantly, having multiple established risk factors does not necessarily mean the individual will develop pancreatic cancer. A substantial proportion develop pancreatic cancer without having any risk factor apart from increasing age.

The number or exposed among the whole pancreatic cancer population, their attributable fractions and the evidence grade is summarized in Table 1.1. The evidence grading is presented in Table 1.2 and terms related to studies and outcomes are presented in Table 1.3.

Table 1.1 Risk factors for pancreatic cancer

Association	Risk factors	Exposed	Attributable fraction	Evidence
High risk (RR ≥ 2.0)	Chronic and hereditary pancreatitis	<1%	< 3%	Strong
Moderate risk (RR 1.5–1.9)	Tobacco smoking	25–40%	11–32%	Strong
	Diabetes mellitus	4–17%	1–16%	Strong
	Family history	5–10%	3–7%	Strong
	Acute pancreatitis	.	.	Weak
	Poor oral hygiene	.	.	Strong
Low risk (RR 1.1–1.4)	Obesity	20–40%	3–16%	Strong
	High alcohol consumption	5–20%	< 9%	Strong
	Non-O blood group	50–60%	13–19%	Strong
	Western dietary pattern	.	.	Weak
Low to moderate protection (RR 0.5–0.9)	Healthy dietary pattern	.	.	Moderate
	Allergy	10–20%	3–7%	Strong

Adapted and modified from Maisonneuve et al. [1]

1.2 Age, Gender and Race

The probability of developing pancreatic cancer is approximately 1% over a lifetime. As with most cancer forms, the risk of developing pancreatic cancer increases with increasing age. The median age at diagnosis is 72 years and over 90% of cases are diagnosed after 50 years of age [2].

Men have a higher incidence of pancreatic cancer compared to women (incidence ratio 1.1–2.0) (Wahi). Studies of hormonal causal risk factors for the disease have been inconclusive [3, 4]. Thus, the difference between sexes is likely attributable to differences in prevalence of other risk factors such as smoking, heavy alcohol intake and obesity.

American epidemiological studies report an increased risk in African Americans compared to the Caucasian population (1.4-fold higher incidence) [5]. Similarly, Native Hawaiians and Japanese Americans also have a higher risk compared to European Americans, after adjusting for other established risk factors [6].

Table 1.2 Evidence grading used in this chapter [1]

Strong evidence	Supported by more than one meta-analysis and confirmed in cohort studies or by a pooled analysis
Moderate evidence	Supported by more than one meta-analysis or a single meta-analysis of cohort studies
Weak evidence	Support from a single meta-analysis not based exclusively on results from cohort studies or if reports are inconclusive

Table 1.3 Terms related to type of studies and outcomes

Term	Explanation
Cohort study	The risk factor and disease are analyzed in a population or group of individuals with a shared characteristic. Risk increase is presented as relative risk
Case–control study	The risk factor is measured in individuals having the outcome and compared with individuals without the outcome. Risk increase is presented as an odds ratio
Meta-analysis	A systematic analysis of previous published studies addressing the same research question. Provides higher statistical power and more robust estimates
Pooled analysis	Combines the results of multiple individual studies. Requires that the included studies are homogenous with regards to population, study design and statistical methods
Relative risk	The ratio of the probability of an outcome in individuals with the risk factor vs the probability of the outcome in individuals without the risk factor of interest
Association	The risk factor and the outcome are significantly linked with each other. The link might be because the risk factor causes the outcome but it might also be due to systemic bias, unknown confounders, reverse causality (that the outcome causes the risk factor) or by mere chance
Causation	The risk factor causes the outcome. In epidemiology, this is difficult to prove. Causality is more likely when associations are strong and when individual study results are consistent (among other criteria for assessing causality in epidemiological studies)
Confounder	A factor that affects both the risk factor of interest and the outcome. If known and measured, statistical models can adjust for confounders

1.3 Pancreatitis (Acute, Chronic and Hereditary)

Inflammation predisposes to the initiation and development of cancer [7]. Inflammation of the pancreas parenchyma can be of acute or chronical character and both are associated with a higher risk of pancreatic cancer. In mice carrying a *KRAS* mutation, pancreatitis induction lead to a non-resolving inflammatory state that causes progression of premalignant PanIN-lesions and accelerates pancreatic cancer development [8, 9].

1.3.1 Chronic Pancreatitis

The evidence for chronic pancreatitis as a risk factor is strong, but since it is a relatively rare condition, the attributable fraction is low [1]. The association is strongest when the lag-time is short, i.e. when pancreatic cancer is diagnosed within 2 years from the chronic pancreatitis diagnosis (relative risk 16.0) and the risk decreases with increasing follow-up time [10]. This might reflect reverse causality due to tumor obstruction of the duct system or mistaking pancreatic cancer for chronic pancreatitis on radiology. However, there still is a strong risk association with longer follow-up suggesting that chronic inflammation of the pancreas drives carcinogenesis. At 5 and 9 years between the chronic pancreatitis and pancreatic cancer diagnosis, the relative risk is 7.9 and 3.5 respectively [10]. Similar results have been reported in another pooled analysis of >15,000 pancreatitis patients. The odds ratio was 13.6 for developing pancreatic cancer within 2 years of the chronic pancreatitis diagnosis and 2.7 if diagnosed more than 2 years after the pancreatitis diagnosis. To clarify, this analysis did not separate between acute and chronic pancreatitis [11]. Surveillance for pancreatic cancer in chronic pancreatitis patients is not supported since only ~5% of chronic pancreatitis patients actually develop pancreatic cancer [12].

1.3.2 Acute Pancreatitis

Acute pancreatitis is also associated with an increased risk of pancreatic cancer but results are conflicting and the evidence is weak. Similar to chronic pancreatitis it can be a manifestation of pancreatic cancer [13], which is important to consider in search of the etiology behind an acute pancreatitis diagnosis. The risk is highest (2–20-fold) during the first 1–2 years after acute pancreatitis and then declines gradually over time [14–17]. However, the risk increase remains after 5 years of follow-up with an approximately twofold increased risk in case–control studies [14, 16]. Whether there is a true increased risk has been debated since other studies found no associated risk after 10 years of follow-up [15, 18]. The most recent well-performed study found a twofold risk increase after 10 years of follow up. The absolute risk was 0.7% at 2 years and 0.87% after 5 years of follow up [16].

1.3.3 Hereditary Pancreatitis

Hereditary pancreatitis is a rare form of chronic pancreatitis that is most commonly due to autosomal dominant inherited mutations in the trypsinogen (*PRSS1*) gene causing premature trypsin activation and parenchymal injury [19]. The median age of symptom onset is 12 years [19]. Hereditary pancreatitis is associated with early premalignant dysplastic lesions in the pancreas (PanINs) [20] and a high risk of developing pancreatic cancer. The cumulative incidence is 3.4–10% at 50 years of age and 18.8–50% at 70–75 years of age [19, 21, 22]. Avoidance of smoking and alcohol is recommended for individuals with hereditary pancreatitis and yearly radiological surveillance has been advocated from 40 years of age [23] although no study has evaluated the efficacy of this approach. In hereditary pancreatitis there is an increased risk of pancreatic cancer with time from symptom onset [19] in contrast to acute and chronic pancreatitis. This might be due to differences in cancer development from the two conditions (assuming a causal relationship), differences in the underlying etiology of the inflammatory state (extrinsic vs. intrinsic) or reverse causality in the case of chronic pancreatitis that might be misdiagnosed pancreatic cancer.

1.4 Tobacco Smoking

Long term smoking leads to an approximately doubled increased risk of pancreatic cancer supported by multiple studies and pooled analyses. The evidence is strong. Since smoking is common it is the risk factor that contributes most to pancreatic cancer incidence [1]. In a 2018 meta-analysis of 78 studies the pooled relative risk was 1.8 for current smokers and 1.1–1.2 for former smokers [24]. Pooled data from multiple case–control studies approximate an odds ratio of 1.77–2.2 for current smokers [25, 26]. Higher intensity and longer smoking duration increased the risk in these reports, while smoking cessation abolished the risk after 15–20 years of cessation. Cigar smoking has similar odds ratio compared to cigarette smoking, but is less studied [27]. Environmental tobacco smoke exposure is not associated with an increased risk in pancreatic cancer development [28].

While an association between pancreatic cancer and smokeless tobacco have been reported, meta-analyses and a recent pooled analysis of cohort studies report inconclusive results or no significant risk increase [29–31].

1.5 Alcohol Consumption

Heavy alcohol consumption is associated with an increased risk for pancreatic cancer. The relative risk was 1.15 for intake of ~24 g alcohol daily (~2 drinks/day) and higher when considering liquor only (relative risk 1.43). There is no evidence for any increased risk for individuals with a low to moderate alcohol consumption

[32–35]. Importantly, heavy alcohol consumption can cause acute and chronic pancreatitis which in turn increase the risk of pancreatic cancer and most studies have not adjusted for these confounders [34]. In support of a true risk association, a pooled analysis of case–control studies reported a consistent increased risk for consumers of ≥6 drinks per day when excluding pancreatitis patients [33]. In addition, the prevalence of pancreatitis is low even among heavy alcohol consumers [33].

1.6 Body Mass Index and Obesity

Obesity is associated with an increased risk of several cancer forms including pancreatic cancer [36]. The pooled relative risk from multiple prospective studies is ~1.10–1.12 for each five unit increase in BMI [37–39]. Central obesity measured by waist-to-hip ratio and waist circumference is also positively associated with increased pancreatic cancer mortality independent of BMI [37, 40]. In addition, there is support of a causal association between BMI and pancreatic cancer from Mendelian randomization studies (explained in Box 1.1) [41, 42], highlighting obesity as an important modifiable risk factor for the disease.

Box 1.1 Mendelian Randomization

In epidemiological risk factor studies there is always a risk that the results are due to unmeasured confounding factors or reverse causality. Mendelian randomization is a method that tries to overcome these problems by using genetic variants that affect the outcome only through the risk factor of interest. This is possible as genetic variants are inherited independent of potential confounding factors, with alleles being randomly allocated at conception. The effect can be viewed as a genetic randomised controlled trial (Fig. 1.1). A simple example is the use genetic variants of the alcohol dehydrogenase gene (*ALDH2*) to explain the risk association between alcohol (exposure) and blood pressure (outcome). Individuals with certain *ALDH2* variants have a considerably lower tolerance for alcohol (i.e. the genetic variant is robustly associated with the exposure) and if these individuals have lower blood pressure, this suggest that lower alcohol consumption leads to lower blood pressure. This assumes that there is no direct association between *ALDH2* and blood pressure [43]. Instead of a single gene variation, Mendelian randomization studies often use associations between a risk factor and multiple genetic variants or single nucleotide polymorphism (SNPs) derived from large-scale genome wide association studies (GWAS). The studies referred to in this chapter have used genetic variants and SNPs from GWAS data to draw conclusions about causal relationships between BMI, obesity, dyslipidemia and diabetes mellitus type 2 [41, 42]

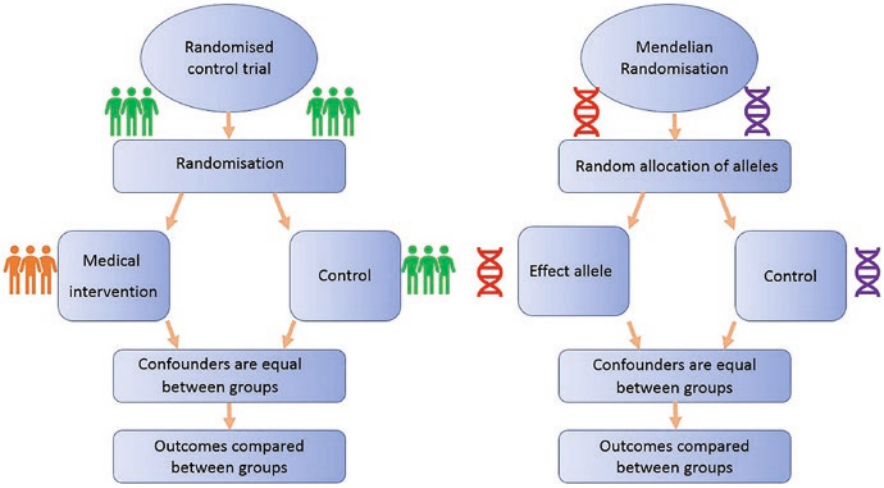

Fig. 1.1 Mendelian randomization studies can be compared with a randomized controlled trial. Instead of randomization to an intervention, alleles are randomly allocated at conception. (Original figure from Howell et al. {Howell, 2018 #106} Copyright © 2018 Howell, Zheng, Haycock, McAleenan, Relton, Martin and Kurian)

1.7 Diabetes Mellitus

Both young-onset/type I and type II diabetes have been associated with pancreatic cancer but only the association with type II diabetes has supporting strong evidence [44]. At diagnosis, a majority of pancreatic cancer patients have hyperglycemia or diabetes, and only 14% have a normal fasting glucose [45]. Similar to pancreatitis, long term diabetes is a risk factor but diabetes can also be the first manifestation of the disease and the relative risk is higher close to the pancreatic cancer diagnosis. The overall relative risk of pancreatic cancer in individuals with diabetes is almost doubled [46, 47]. The risk association is stronger in pancreatic cancer patients with short-term diabetes, and highest for individuals who are diagnosed with diabetes within 1 year prior to pancreatic cancer diagnosis (relative risk 5.4) [46]. Fasting glucose elevations present at 36–30 months prior to diagnosis and fasting glucose levels are positively associated with tumor volume at diagnosis [48]. This likely reflects reverse causality, i.e. that the tumor somehow causes diabetes (Box 1.2). In support, surgical removal of the tumor improves the hyperglycemic status in half of the patients and a Mendelian randomization study did not support a causal relationship between long standing diabetes mellitus and pancreatic cancer [41]. Screening and surveillance are limited by the high prevalence of diabetes and low incidence of pancreatic cancer. Less than 1% of individuals diagnosed with diabetes develop pancreatic cancer within 3 years [49].

Box 1.2 Does Pancreatic Cancer Cause Hyperglycemia?
How pancreatic cancer causes hyperglycemia is not completely understood. Experimental studies have tried to assess an eventual paraneoplastic phenomenon. A possible mediator is the protein adrenomedullin that has been shown to inhibit insulin secretion from beta-cells in cell culture [50]. Pancreatic cancer cells shed microparticles called exosomes containing adrenomedullin, which is also found in plasma from pancreatic cancer patients. These exosomes can be internalized into beta-cells causing endoplasmic reticulum stress and inhibition of insulin secretion [51]. It is also possible that pancreatic cancer cells affect peripheral glucose uptake. Pancreatic cancer cell derived exosomes have been shown to affect insulin resistance in myoblasts cells in cell culture [52].

1.8 Dietary Patterns

A Western dietary pattern is associated with an increased risk of pancreatic cancer and a healthy dietary pattern has been associated with a decreased risk. The evidence is weak to moderate and the results from current meta-analyses should be interpreted with caution. The Western dietary pattern is characterized by red meat, processed meat, sweets, high fat food, potatoes and low amounts of fruits and vegetables. The healthy diet is characterized by high amounts of vegetables and fruits, whole grains, olive oil, fish, poultry and low-fat foods. Importantly, meta-analyses of the risk between diet and pancreatic cancer show inconsistent results, and significant associations are almost exclusively found in case–control studies (weak or no associations in cohort studies), which indicates potential bias [53, 54]. The included studies have been adjusted for age, sex, diabetes, BMI, smoking and total energy intake. Only three studies have been adjusted for social status or education [53, 54]. A meta-analysis including prospective studies reported an increased risk of pancreatic cancer for consumers of >50 g of processed meat per day (RR 1.19) and male consumers of red meat (RR 1.29) [55]. The possible protective effect of fruits and vegetables has been suggested to be due to dietary fibers and antioxidant substances including vitamin C, which have been suggested to protect from inflammatory processes. The risk association with red and processed meats might be due to increased intake of hem iron, nitrite and heterocyclic amines—all of which have been suggested as potential carcinogens in experimental studies [53].

1.9 Poor Oral Hygiene

Studies on oral hygiene show an association between periodontal (gum) disease and edentulism (tooth loss) and pancreatic cancer. The evidence is strong. Meta-analyses associate periodontal disease with a 1.74 relative risk and edentulism

with a 1.54 relative risk for pancreatic cancer [56, 57]. Periodontal disease and pancreatic cancer share several risk factors (including obesity, tobacco smoking, diabetes, alcohol consumption and allergy) but these confounders were adjusted for in most studies included in meta-analyses [56, 57]. The link between oral hygiene and pancreatic cancer is unclear, but might be linked to alterations in the oral microbiome that contribute to systemic inflammation. Studies of the oral microbiota show that presence of oral bacterial pathogens increase the risk of pancreatic cancer, while commensal flora decrease the risk [58, 59]. In addition, a recent study described the presence of oral pathogens in premalignant IPMN cyst fluid [60], indicating that these pathogens might be involved in early pancreatic cancer development.

1.10 ABO Blood Group

ABO genotype is associated with pancreatic cancer risk and the evidence is strong. Having another blood group than type O is associated with an increased risk of pancreatic cancer, supported by two meta-analyses and a large case–control study [61–63]. In addition, there is a lower frequency of type O blood group in pancreatic cancer patients compared to patients with other cancer forms, suggesting that the association is specific for pancreatic ductal adenocarcinoma [61].

1.11 Potential Risk Factors

In addition, there are several reports on risk associations where the evidence is weak or inconclusive. Environmental exposures including chlorinated hydrocarbon solvents, ionizing radiation, nickel, lead, cadmium, arsenic and formaldehyde have all been associated with an increased risk but the results are supported by single studies [1, 64].

Similarly, risk associations with gut microbiome have been reported in only a few studies [65]. Risk factors where the results are inconclusive include Hepatitis B and C infection, Styrene (used in plastic products), *H. pylori* infection, physical inactivity, vitamin D intake and cholecystectomy [1, 64–66].

1.12 Study Design and Ongoing Epidemiological Projects

Inherited rare mutations such as Li-Fraumeni and Peutz-Jaegers confer a high risk of pancreatic cancer but account for a small proportion of patients. A larger proportion of individuals carry genomic variants with low penetrance that are associated with pancreatic cancer, identified in genome-wide association studies (GWAS). GWAS are observational studies that can pinpoint association between genomic variants and disease and are typically focused on single-nucleotide polymorphisms

(SNP). The pancreatic cancer cohort consortium (PanScan) and the pancreatic cancer case–control consortium (PanC4) have published a number of reports on GWAS studies on individuals of European ancestry and have identified 13 genomic loci associated with pancreatic cancer [67–71]. The PANcreatic Disease ReseArch (PANDoRA) case–control consortium identified one additional risk locus [72]. A meta-analysis of the aforementioned studies could identify five additional risk loci [73]. To identify genes that mediate the effects of genomic variants, GWAS data can be combined with gene expression data in transcriptome-wide association studies and such studies have identified several candidate genes associated with pancreatic cancer risk [74, 75]. GWAS studies on individuals of Asian ancestry have identified eight genomic risk loci, with limited overlap with findings on European populations, suggesting that genomic variants and pancreatic cancer risk associations differ depending on the ancestry of the source population [72, 76, 77]. GWAS, TWAS and Mendelian randomization studies, utilizing genomic data to provide insight in susceptibility genes and risk factor causality are likely to provide novel insight in pancreatic cancer risk stratification in the future.

1.13 Conclusions

There are several modifiable risk factors for pancreatic cancer but the independent risk associations are generally modest. Screening for pancreatic cancer in these risk populations is therefore generally not recommended. The risk factor that contributes most is cigarette smoking due to its high prevalence in the general population. Having multiple risk factors contributes to an elevated risk for pancreatic cancer, as well as other cancer forms and cardiovascular disease. To summarize current recommendations for reducing the risk of developing pancreatic cancer, it is advisable to refrain from smoking and heavy alcohol consumption, to maintain a healthy weight and include vegetables and fruit in the diet. Genomic data are increasingly integrated in risk association studies to account for confounders and gain insight in risk loci and genes associated with pancreatic cancer. The clinician should be well aware of the increased risk of pancreatic cancer in patients with pancreatitis and new-onset diabetes mellitus.

References

1. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015;44(1):186–98.
2. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010;28(4–5):645–56.
3. Heuch I, Jacobsen BK, Albrektsen G, Kvale G. Reproductive factors and pancreatic cancer risk: a Norwegian cohort study. Br J Cancer. 2008;98(1):189–93.
4. Wahi MM, Shah N, Schrock CE, Rosemurgy AS II, Goldin SB. Reproductive factors and risk of pancreatic cancer in women: a review of the literature. Ann Epidemiol. 2009;19(2):103–11.

5. Cervantes A, Waymouth EK, Petrov MS. African-Americans and indigenous peoples have increased burden of diseases of the exocrine pancreas: a systematic review and meta-analysis. Dig Dis Sci. 2019;64(1):249–61.
6. Huang BZ, Stram DO, Le Marchand L, Haiman CA, Wilkens LR, Pandol SJ, et al. Interethnic differences in pancreatic cancer incidence and risk factors: the Multiethnic Cohort. Cancer Med. 2019;8(7):3592–603.
7. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity. 2019;51(1):27–41.
8. Carriere C, Young AL, Gunn JR, Longnecker DS, Korc M. Acute pancreatitis accelerates initiation and progression to pancreatic cancer in mice expressing oncogenic Kras in the nestin cell lineage. PLoS One. 2011;6(11):e27725.
9. Kong B, Bruns P, Behler NA, Chang L, Schlitter AM, Cao J, et al. Dynamic landscape of pancreatic carcinogenesis reveals early molecular networks of malignancy. Gut. 2018;67(1):146–56.
10. Kirkegard J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol. 2017;112(9):1366–72.
11. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23(11):2964–70.
12. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24(3):349–58.
13. Li S, Tian B. Acute pancreatitis in patients with pancreatic cancer: timing of surgery and survival duration. Medicine (Baltimore). 2017;96(3):e5908.
14. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. Gastroenterology. 1995;109(1):247–51.
15. Karlson BM, Ekbom A, Josefsson S, McLaughlin JK, Fraumeni JF Jr, Nyren O. The risk of pancreatic cancer following pancreatitis: an association due to confounding? Gastroenterology. 1997;113(2):587–92.
16. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, Mortensen FV. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. Gastroenterology. 2018;154(6):1729–36.
17. Munigala S, Kanwal F, Xian H, Scherrer JF, Agarwal B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. Clin Gastroenterol Hepatol. 2014;12(7):1143–50.e1.
18. Sadr-Azodi O, Oskarsson V, Discacciati A, Videhult P, Askling J, Ekbom A. Pancreatic cancer following acute pancreatitis: a population-based matched cohort study. Am J Gastroenterol. 2018;113(11):1711–9.
19. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004;2(3):252–61.
20. Rebours V, Levy P, Mosnier JF, Scoazec JY, Soubeyrand MS, Flejou JF, et al. Pathology analysis reveals that dysplastic pancreatic ductal lesions are frequent in patients with hereditary pancreatitis. Clin Gastroenterol Hepatol. 2010;8(2):206–12.
21. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442–6.
22. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Maire F, Hammel P, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. Am J Gastroenterol. 2008;103(1):111–9.
23. Ulrich CD, Consensus Committees of the European Registry of Hereditary Pancreatic Diseases MM-CPSGIAoP. Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. Pancreatology. 2001;1(5):416–22.
24. Lugo A, Peveri G, Bosetti C, Bagnardi V, Crippa A, Orsini N, et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: a comprehensive review and meta-analysis. Eur J Cancer. 2018;104:117–26.

25. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol. 2012;23(7):1880–8.
26. Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol. 2009;170(4):403–13.
27. Bertuccio P, La Vecchia C, Silverman DT, Petersen GM, Bracci PM, Negri E, et al. Cigar and pipe smoking, smokeless tobacco use and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2011;22(6):1420–6.
28. Zhou J, Wellenius GA, Michaud DS. Environmental tobacco smoke and the risk of pancreatic cancer among non-smokers: a meta-analysis. Occup Environ Med. 2012;69(12):853–7.
29. Araghi M, Rosaria Galanti M, Lundberg M, Lager A, Engstrom G, Alfredsson L, et al. Use of moist oral snuff (snus) and pancreatic cancer: pooled analysis of nine prospective observational studies. Int J Cancer. 2017;141(4):687–93.
30. Gupta S, Gupta R, Sinha DN, Mehrotra R. Relationship between type of smokeless tobacco & risk of cancer: a systematic review. Indian J Med Res. 2018;148(1):56–76.
31. Sponsiello-Wang Z, Weitkunat R, Lee PN. Systematic review of the relation between smokeless tobacco and cancer of the pancreas in Europe and North America. BMC Cancer. 2008;8:356.
32. Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomark Prev. 2009;18(3):765–76.
33. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol. 2012;23(2):374–82.
34. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer. 2010;126(6):1474–86.
35. Wang YT, Gou YW, Jin WW, Xiao M, Fang HY. Association between alcohol intake and the risk of pancreatic cancer: a dose-response meta-analysis of cohort studies. BMC Cancer. 2016;16:212.
36. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.
37. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23(4):843–52.
38. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer. 2003;89(3):519–23.
39. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. Int J Cancer. 2007;120(9):1993–8.
40. Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol. 2015;26(11):2257–66.
41. Carreras-Torres R, Johansson M, Gaborieau V, Haycock PC, Wade KH, Relton CL, et al. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a Mendelian randomization study. J Natl Cancer Inst. 2017;109(9):djx043.
42. Langdon RJ, Richmond RC, Hemani G, Zheng J, Wade KH, Carreras-Torres R, et al. A phenome-wide Mendelian randomization study of pancreatic cancer using summary genetic data. Cancer Epidemiol Biomark Prev. 2019;28(12):2070–8.
43. Davies NM, Holmes MV, Davey SG. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
44. Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. Br J Cancer. 2007;96(3):507–9.

45. Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008;134(4):981–7.
46. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47(13):1928–37.
47. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92(11):2076–83.
48. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. Gastroenterology. 2018;155(2):490–500.e2.
49. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology. 2005;129(2):504–11.
50. Aggarwal G, Ramachandran V, Javeed N, Arumugam T, Dutta S, Klee GG, et al. Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulin resistance in beta cells and mice. Gastroenterology. 2012;143(6):1510–7.e1.
51. Javeed N, Sagar G, Dutta SK, Smyrk TC, Lau JS, Bhattacharya S, et al. Pancreatic cancer-derived exosomes cause paraneoplastic beta-cell dysfunction. Clin Cancer Res. 2015;21(7):1722–33.
52. Wang L, Zhang B, Zheng W, Kang M, Chen Q, Qin W, et al. Exosomes derived from pancreatic cancer cells induce insulin resistance in C2C12 myotube cells through the PI3K/Akt/FoxO1 pathway. Sci Rep. 2017;7(1):5384.
53. Lu PY, Shu L, Shen SS, Chen XJ, Zhang XY. Dietary patterns and pancreatic cancer risk: a meta-analysis. Nutrients. 2017;9(1):38.
54. Zheng J, Guinter MA, Merchant AT, Wirth MD, Zhang J, Stolzenberg-Solomon RZ, et al. Dietary patterns and risk of pancreatic cancer: a systematic review. Nutr Rev. 2017;75(11):883–908.
55. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106(3):603–7.
56. Maisonneuve P, Amar S, Lowenfels AB. Periodontal disease, edentulism, and pancreatic cancer: a meta-analysis. Ann Oncol. 2017;28(5):985–95.
57. Corbella S, Veronesi P, Galimberti V, Weinstein R, Del Fabbro M, Francetti L. Is periodontitis a risk indicator for cancer? A meta-analysis. PLoS One. 2018;13(4):e0195683.
58. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut. 2018;67(1):120–7.
59. Michaud DS, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjonneland A, et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut. 2013;62(12):1764–70.
60. Gaiser RA, Halimi A, Alkharaan H, Lu L, Davanian H, Healy K, et al. Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer. Gut. 2019;68(12):2186–94.
61. Iodice S, Maisonneuve P, Botteri E, Sandri MT, Lowenfels AB. ABO blood group and cancer. Eur J Cancer. 2010;46(18):3345–50.
62. Risch HA, Lu L, Wang J, Zhang W, Ni Q, Gao YT, et al. ABO blood group and risk of pancreatic cancer: a study in Shanghai and meta-analysis. Am J Epidemiol. 2013;177(12):1326–37.
63. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res. 2010;70(3):1015–23.
64. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: an update. Arch Toxicol. 2016;90(11):2617–42.
65. Tsai HJ, Chang JS. Environmental risk factors of pancreatic cancer. J Clin Med. 2019;8(9):1427.
66. Collins JJ, Delzell E. A systematic review of epidemiologic studies of styrene and cancer. Crit Rev Toxicol. 2018;48(6):443–70.
67. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet. 2009;41(9):986–90.

68. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010;42(3):224–8.
69. Wolpin BM, Rizzato C, Kraft P, Kooperberg C, Petersen GM, Wang Z, et al. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. Nat Genet. 2014;46(9):994–1000.
70. Zhang M, Wang Z, Obazee O, Jia J, Childs EJ, Hoskins J, et al. Three new pancreatic cancer susceptibility signals identified on chromosomes 1q32.1, 5p15.33 and 8q24.21. Oncotarget. 2016;7(41):66328–43.
71. Childs EJ, Mocci E, Campa D, Bracci PM, Gallinger S, Goggins M, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. Nat Genet. 2015;47(8):911–6.
72. Campa D, Rizzato C, Stolzenberg-Solomon R, Pacetti P, Vodicka P, Cleary SP, et al. TERT gene harbors multiple variants associated with pancreatic cancer susceptibility. Int J Cancer. 2015;137(9):2175–83.
73. Klein AP, Wolpin BM, Risch HA, Stolzenberg-Solomon RZ, Mocci E, Zhang M, et al. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. Nat Commun. 2018;9(1):556.
74. Gong L, Zhang D, Lei Y, Qian Y, Tan X, Han S. Transcriptome-wide association study identifies multiple genes and pathways associated with pancreatic cancer. Cancer Med. 2018;7(11):5727–32.
75. Zhong J, Jermusyk A, Wu L, Hoskins JW, Collins I, Mocci E, et al. A Transcriptome-Wide Association Study (TWAS) identifies novel candidate susceptibility genes for pancreatic cancer. J Natl Cancer Inst. 2020.
76. Low SK, Kuchiba A, Zembutsu H, Saito A, Takahashi A, Kubo M, et al. Genome-wide association study of pancreatic cancer in Japanese population. PLoS One. 2010;5(7):e11824.
77. Wu C, Miao X, Huang L, Che X, Jiang G, Yu D, et al. Genome-wide association study identifies five loci associated with susceptibility to pancreatic cancer in Chinese populations. Nat Genet. 2011;44(1):62–6.

Chapter 2
Epidemiology of Pancreatic Cancer

Gerald Haidinger

Take Home Messages

- Regarding overall incidence, pancreatic cancer is a less common cancer globally.
- Due to its high case fatality, it ranks seventh in worldwide cancer mortality.
- As a result of the worldwide increase of lifespan it can be expected that incidence and mortality will rise further globally.
- Major risk factors associated with pancreatic cancer, such as smoking, diabetes and obesity are potentially modifiable, providing excellent opportunity for prevention.

Pearls and Pitfalls

- Age is a very important risk factor for cancer, hence, aging populations will drive the increase in incidence.
- As other countries strive to increase their productivity and economic prosperity it can be expected that this will also influence life expectancy and percentage of overweight in their population.

Further Perspectives

- Health statistics are vital for international comparison.
- Differences in incidence, survival and mortality between countries or regions are influenced by means for cancer detection, the quality of cancer registries, medical therapy and cause-of-death notification in the single countries.

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2.1 Introduction

Pancreatic cancer is ranks as the 12th most common malignancy, with an estimated 459,000 new cases globally in 2018 [1]. This corresponds to 2.5% of all new cancer cases worldwide. The small difference between the number of new cases and the number of deaths (an estimated 432,000) from this cancer confirms the poor prognosis of this disease (Fig. 2.1). This puts pancreatic cancer in the seventh rank (4.5%) in global cancer mortality after cancers of the lung, stomach and liver, breast, colon, and oesophagus [1]. The epidemiological characteristics (Box 2.1) of pancreatic cancer makes it nonetheless a public health burden, as a cancer with a very high case-fatality rate as the incidence and mortality almost approaches 100%. This chapter will detail some epidemiological features of pancreatic cancer worldwide, with examples from selected countries and regions.

2.2 Worldwide Incidence

Considering the geographical distribution, the highest age-standardized rates of incidence are found in the high-income regions of the world (North America, Western Europe, Asia Pacific and Central Europe [2]. The age-standardised incidence rate was 5.0/100,000 (4.9–5.1/100,000) in 1990 and increased to 5.7/100,000 (5.6–5.8/100,000, World Standard Population) in 2017 [2]. The highest incidence is observed in high income countries (Fig. 2.2), showing a positive correlation with

Box 2.1 Definition of Terms

Incidence: The number of new cases of a disease within a timespan (usually 1 year) gives information about the hazardousness and about the spreading of a disease, usually expressed as a number relative to the population.

Prevalence: The total number of cases living with a certain disease (within a region or a country and within a timespan, also usually calculated for one specific year), usually expressed as a number relative to the population.

Morbidity: The number of cases living with a certain disease irrespective of the time of onset (can not be calculated, is sort of a summative term if one does not want to differentiate between incidence and prevalence).

Mortality: The number of deaths from a certain disease (or group of diseases, e.g. "cardiovascular mortality"), usually expressed as a number relative to the population.

Case-fatality (Lethality): The number of deaths from a specific disease relative to the number of cases gives information about the deadliness of a disease, usually expressed as a percentage.

Fig. 2.1 Incidence and mortality of pancreatic cancer in Austria, 1983–2016, age standardized. (Data source: Statistics Austria, 2019 [5])

the Human Development Index (HDI), as well as with the Gross Domestic Product (GDP) of a country [3]. The highest incidence is found in Eastern Europe (males 9.9/100,000, females 5.8/100,000) and Western Europe (males 9.5/100,000, females 7.2/100,000), followed by Northern America (males 8.7/100,000, females 6.5/100,000), and Southern Europe (males 8.6/100,000, females 5.9/100,000), the lowest in Western Africa (males 2.4/100,000, females 1.9/100,000), Eastern Africa (males 1.4/100,000, females 1.4/100,000), and South Central Asia (males 1.1/100,000, females 1.0/100,000; all numbers: year 2018, age-adjusted to the World Standard Population) [1]. Figure 2.2 shows the incidence (n/100,000) of pancreatic cancer by World Areas, sorted by incidence in females [4].

2.3 Trends in Incidence

Trend analysis of incidence shows a small but steady increase of incidence globally. The number of incident cases of pancreatic cancer in both sexes increased 2.3 times from 195,000 incident cases in 1990 to 448,000 cases in 2017 globally [2].

The sex distribution globally is slightly to the disadvantage of men, in 2017, 51.9% (232,000) of the total incident cases occurred in males, compared with 52.1% (102,000) in 1990 [2]. The number of incident cases peaked at the ages of 65–69 years in males, whereas the peak in females was observed at the ages of 75–79 years.

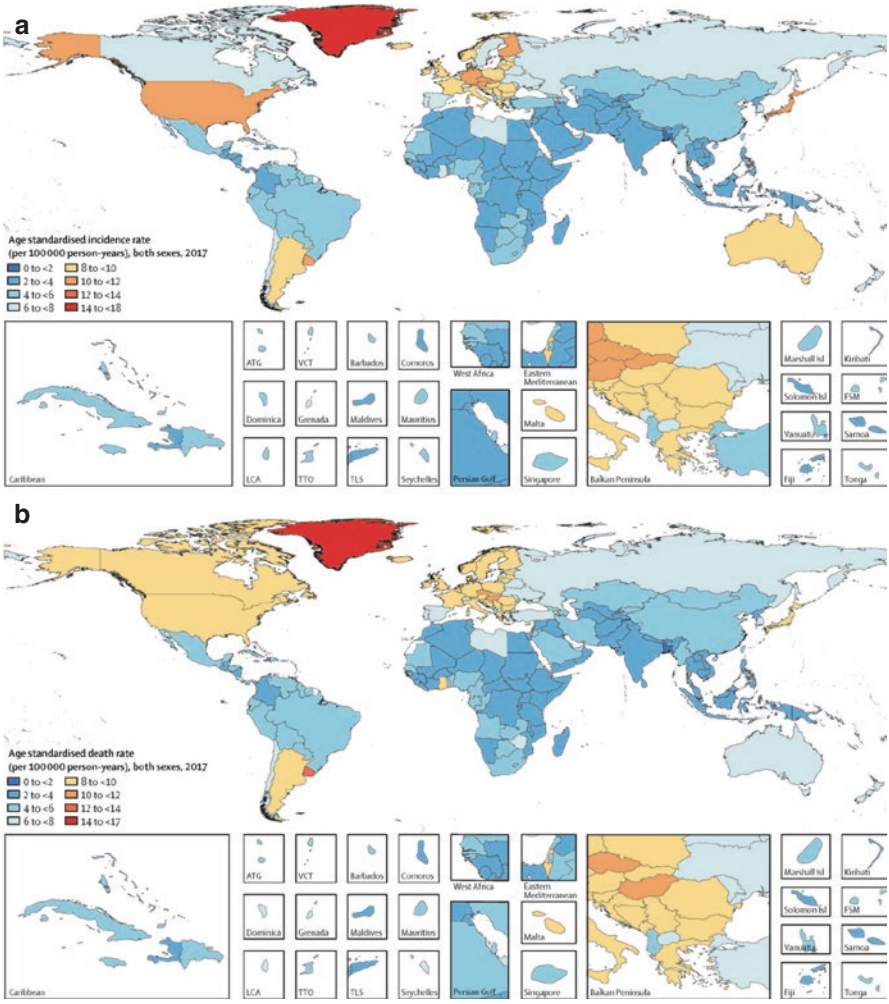

Fig. 2.2 Age-standardised rates of incidence (**a**) and death (**b**) of pancreatic cancer across 195 countries and territories in both sexes, 2017. (Reproduced with permission from GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2019 Dec;4(12):934–947)

2.3.1 Data from The Netherlands

In a Dutch national cohort of 36,453 patients with pancreatic ductal adenocarcinoma (PDAC), the incidence increased from 12.1 (1997–2000) to 15.3 (2013–2016) per 100,000, whereas median overall survival increased from 3.1 to 3.8 months. Resection rates and use of adjuvant or palliative chemotherapy increased with

improved survival in these patients. Since the majority of patients only received supportive care, in all patients with PDAC the survival benefit of 3 weeks was negligible [5].

2.3.2 Data from Austria

Pancreatic cancer ranks sixth in the list of the most common cancers in Austria, representing 2.3% of the total incidence of cancer of roughly 41,000 cases (population 2016: 8.7 million) [6].

The number of newly diagnosed cases in Austria rose from 1045 in 1983 to 1799 in 2016, an increase of 72% within these 34 years. This corresponds to age-standardised rates of 18.0 per 100,000 in 1983 to 21.1 per 100,000 in 2016 (males: 20.9 in 1983–22.5 in 2016; females: 15.8 in 1983–19.8 in 2016, European Standard Population 2013), also showing a rising trend in incidence over the years [7].

In Austria, the sex distribution is also slightly to the disadvantage of men, age-standardized rates in men are 22.5 per 100,000 in 2016 (20.9 in 1983) compared to 19.8 per 100,000 in women (15.8 in 1983). According to the larger number of women in Austria as a consequence of a high life expectancy, 47.1% (848 in 2016) of the total incident cases occurred in males, compared with 52.9% (951 cases in 2016) in women [7]. In Austria the number of new cases peaks at ages 65–74 in men and at 75–84 in women, while age-specific incidence peaks at age 75–84 years in both sexes [8].

According to the Austrian Cancer Registry, 2660 cases with pancreatic cancer accounted for 0.7% of the total cancer prevalence (Persons living in Austria with cancer in 2016). Of these, 54.5% had their diagnose within the past 3 years, 12.7% within 3–5 years, 14.8% within 5–10 years and only 18% were diagnosed 10 or more years ago.

With respect to the registered tumour stage, only 5.6% of all cases (2014–2016) were at stage "localised" at time of diagnosis, 21.6% were at stage "regional" and 33.0% were at stage "distant", respectively (26.1% were of "unknown" stage and 13.7% of incident cases were DCO, death certificate only) [7].

2.3.3 Data from Canada

A recent publication from Canada [9] describes age-standardized cancer-incidence trends in Canada between 1971 and 2015. The most striking results from these analyses relate to increasing incidence trends among younger adults for breast, colorectal, pancreatic, endometrial and kidney cancers. Obesity is a risk factor for these cancer sites and the rising incidence runs parallel to the growing prevalence of

obesity in recent decades. In addition, increases in pancreatic cancer and non-Hodgkin lymphoma among women, a new finding, was observed [9].

2.3.4 Data from Puerto Rico

In Puerto Rico, between 2011 and 2015, 7.8 per 100,000 persons were diagnosed with pancreatic cancer. Higher rates were observed in men than in women (9.2 vs. 6.7 per 100,000, respectively) and in persons aged 65 years or older (42.7 per 100,000 persons). A lower risk of being diagnosed with pancreatic cancer was seen in Puerto Rico in comparison to in members of several racial/ethnic groups in the US [10].

2.3.5 Data from the USA

In an analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, trends in age-adjusted incidence of Stage IA PDAC between 2004 and 2016 were determined. The incidence of Stage IA PDAC cases diagnosed increased statistically significantly from 2004 to 2016 (annual percent change (APC): 14.5, 95% confidence interval (CI) [11.4, 17.7], $p < 0.001$). During the study period, average age at diagnosis for Stage IA and IB cases declined by 3.5 years (95% CI: 1.2–5.9 years; $p = 0.004$) and 5.5 years (95% CI = 3.4–7.6 years; $p < 0.001$), whereas average age increased for higher-stage cases (by 0.6–1.4 years). Among Stage IA cases the proportion of blacks was smaller (10.2% v. 12.5%), and the proportion of other non-Caucasians was higher compared to higher-stage cases (11.9% v. 8.4%, $p < 0.001$). The 5-year overall survival for Stage IA PDAC improved from 44.7% [95% CI = 31.4, 63.7] in 2004 to 83.7% [95% CI = 78.6%, 89.2%] in 2012; 10-year survival improved from 36.7% [95% CI = 24.1, 55.8] in 2004 to 49.0% [95% CI = 37.2%, 64.6%] in 2007 [11].

The following Fig. 2.3 shows age-specific counts and rates of incident cases (A), deaths (B), and DALYs (C) of pancreatic cancer by sex, 2017, on a global basis (DALYs = disability-adjusted life-years) [2].

2.4 Worldwide Mortality

There were an estimated 9.6 million cases of death in 2018 globally due to cancer [1], 4.5% of which were attributed to pancreatic cancer. Considering the geographical distribution, the highest age-standardized rates of mortality are found in the high-income regions of the world (Central Europe, High-income North America, Western Europe, and Southern Latin-America, the lowest in Oceania, Central

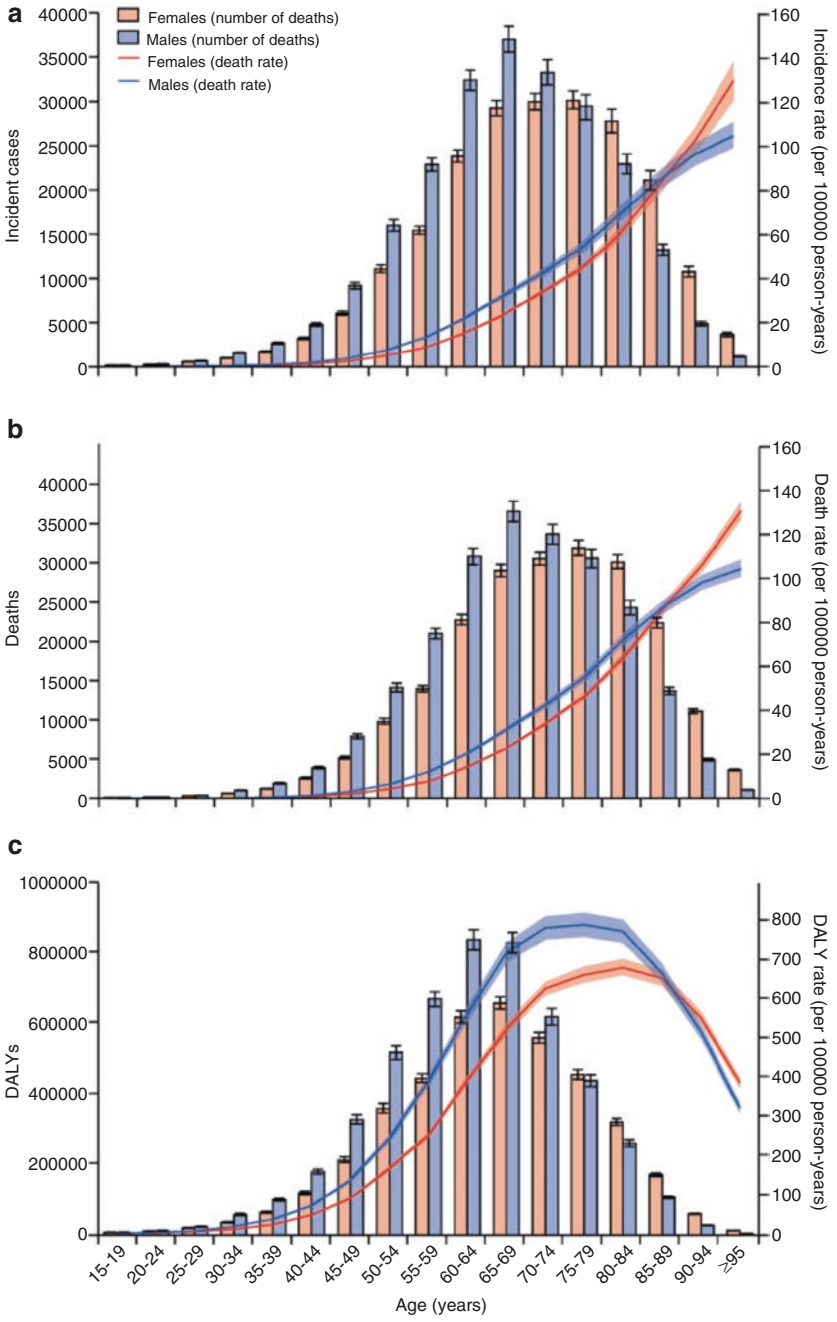

Fig. 2.3 Age-specific counts and rates of incident cases (**a**), deaths (**b**), and DALYs (**c**) of pancreatic cancer by sex, 2017. (Reproduced with permission from GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2019 Dec;4(12):934–947)

sub-Saharan Africa, Eastern sub-Saharan Africa, and South Asia [2].There was a 2.3 times (125%) increase in the number of deaths globally from 1990 to 2017, increasing from 196,000 deaths for both sexes combined in 1990 [2]. The global age-standardised death rate increased by 10.4%, from 5.1/100,000 in 1990 to 5.6/100,000 in 2017. The age-standardised mortality in males was 5.7/100,000 in 1990 and 6.3/100,000 in 2017. The equivalent findings for females were 4.5/100,000 in 1990 and 5.0/100,000 in 2017. In 2017, pancreatic cancer caused approximately 441,000 deaths globally, including roughly 226,000 deaths among males and about 215,000 deaths among females [2].

Age-specific rates for mortality increased with increasing age; this trend was similar between males and females. The number of deaths peaked at the ages of 65–69 years in males, whereas the peak in females was observed at the ages of 75–79 years [2]. Figure 2.3 shows the mortality (n/100,000) of pancreatic cancer by World Areas, sorted by mortality in females [4].

The Fig. 2.4 shows (A) the age-standardised incidence rates of pancreatic cancer in 2017. (B) The percentage change in age-standardised incidence rate of pancreatic cancer from 1990 to 2017. (C) The age-standardised death rates of pancreatic cancer in 2017. (D) The percentage change in age-standardised death rate of pancreatic cancer from 1990 to 2017. GBD = Global Burden of Diseases, Injuries, and Risk Factors Study [2].

2.4.1 Data from The Netherlands

Recent estimates have indicated that the number of deaths from pancreatic cancer overtook breast cancer mortality rates across the EU in 2017, meaning that the disease is now the EU's third leading cause of cancer-related death, behind lung and colorectal cancer [12]. According to GLOBOCAN 2018 [13] pancreatic cancer ranks seventh in women and ninth in men in the Netherlands. Overall, 6.3% of all cancer deaths can be attributed to this cancer. Among the 28 European countries the Dutch mortality ranks 20th.

2.4.2 Data from Austria

Pancreatic cancer ranks third in the list of the most common cancers in Austria, representing 8.6% of the total cancer mortality of roughly 20,000 cases (population 2016: 8.7 million).

The number of deaths due to pancreatic cancer in Austria rose from 1024 in 1983 to 1678 in 2016, an increase of 64% within these 34 years. This corresponds to an increase of age-standardised mortality rates of 17.5/100,000 in 1983 to

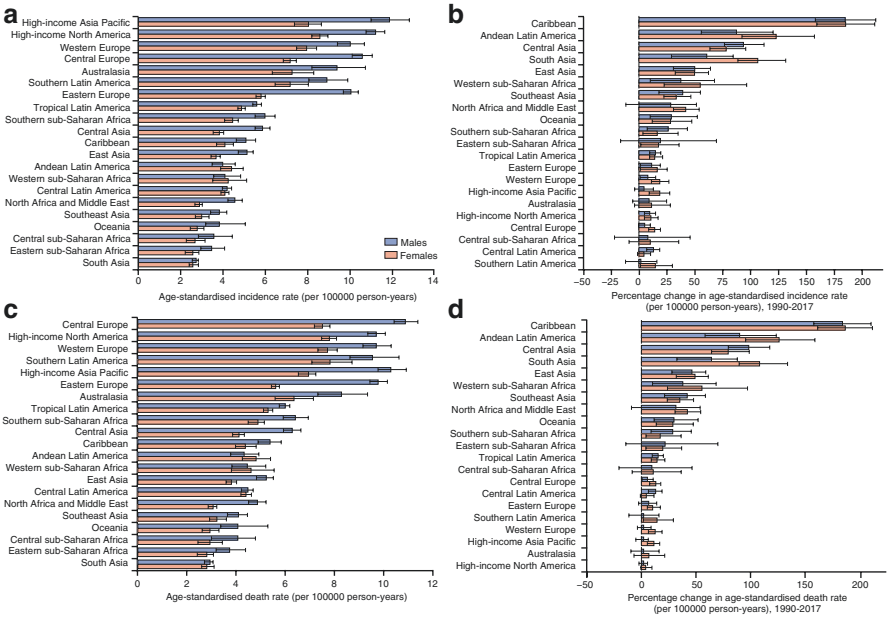

Fig. 2.4 Levels and trends in age-standardised incidence and death rates of pancreatic cancer across 21 GBD regions by sex. (Reproduced with permission from GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2019 Dec;4(12):934–947)

19.6/100,000 in 2016 (males: 20.2 in 1983–21.1 in 2016; females: 15.6 in 1983–18.1 in 2016, European Standard Population 2013), also showing a rising trend in mortality over the years [7].

In Austria, the sex distribution of age-standardized mortality rates is also slightly to the disadvantage of men, nevertheless according to the larger number of women in Austria as a consequence of a high life expectancy, 46.9% (787 in 2016) of the total incident cases occurred in males, compared with 53.1% (991 cases in 2016) in women [7]. In Austria the number of deaths peaks at ages 75–84 in both sexes, while age-specific mortality peaks at age 85+ years in both sexes [8].

A clear increase in 1-year survival can be observed in Austrian patients with pancreatic cancer, rising from 16.7% in the diagnose period 1989–1993 to 37.5% in the diagnose period 2014–2016, and 3-year survival rose from 7.0% in 1989–1993 to 14.6% in 2014–2016. In the survival of longer periods this increase is less pronounced, in the case of 5-year survival the rise is from 5.8% in 1989–1993 to 9.8% in 2014–2016, and the trend of 10-year survival is U-shaped from 5.2% in 1989–1993 to 5.7% in the diagnose period between 2014 and 2016. No distinct differences in survival between men and women can be observed [7].

2.4.3 Data from Canada

Long-term outcomes of Canadian patients affected by PC remain unsatisfactory, with only 9% of the patients surviving at 5 years [14]. The mortality rate is the highest among all the solid tumours with a case-to-fatality ratio of 0.93. The age-standardized 5-year relative survival in 2012 was 9.1% (95% confidence interval [CI], 8.3–10). There were geographic variations among provinces with the highest survival registered in Ontario (10.9%; 95% CI, 9.9–12) and the lowest survival reported in Nova Scotia (4.7%; 95% CI, 2.8–7.2) [14].

2.4.4 Data from Puerto Rico

In Puerto Rico, between 2011 and 2015, 6.7 per 100,000 persons died from pancreatic cancer, men and persons 65 years and older had higher mortality rates. Mortality trends in Puerto Rico increased from 2001 to 2015 (annual percent change [APC] = 1.9%). A lower risk of dying from pancreatic cancer was seen in Puerto Rico compared to members of several racial/ethnic groups in the US [10].

2.4.5 Data from the USA

According to analyses of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, 7.8% of cancer deaths can be attributed to pancreatic cancer (as opposed to 3.2% of cancer incidence). The death rate was 11.0 per 100,000 men and women per year, showing a rather stable trend over the past 25 years [15]. The 5-year relative survival rose from around 2% in the 1970s to 8.6% in the year 2010.

2.5 Conclusion

From an epidemiological point of view, pancreatic cancer is not a very frequent tumour. The substantial case fatality rate makes pancreatic cancer important, however, as number of deaths will soon equal or exceed more common and prevalent cancers. The development of the prevalence of risk factors as well as the further increase in life expectancy will crucially determine the future development of this cancer's incidence and mortality.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. GBD. Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2017;4(2019):934–47.
3. Wong MCS, Jiang JY, Liang M, Fang Y, Yeung MS, Sung JJY. Global temporal patterns of pancreatic cancer and association with socioeconomic development. Sci Rep. 2017;7:3165.
4. International Agency for Research on Cancer. 2020. https://gco.iarc.fr/today/.
5. Latenstein AEJ, van der Geest LGM, Bonsing BA, Groot Koerkamp B, Haj Mohammad N, de Hingh IHJT, de Meijer VE, Molenaar IQ, van Santvoort HC, van Tienhoven G, Verheij J, Vissers PAJ, de Vos-Geelen J, Busch OR, van Eijck CHJ, van Laarhoven HWM, Besselink MG, Wilmink JW, Dutch Pancreatic Cancer Group. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. Eur J Cancer. 2020;125:83–93. https://doi.org/10.1016/j.ejca.2019.11.002. Epub 2019 Dec 13.
6. Statistics Austria, editors. Jahrbuch der Gesundheitsstatistik. Vienna: Statistics Austria; 2019.
7. Statistics Austria. Austrian cancer registry and cause of death statistics. Vienna: Statistics Austria; 2018.
8. Hackl M, Ihle P. Krebserkrankungen in Österreich 2018. Vienna: Statistics Austria; 2018.
9. Brenner DR, Ruan Y, Shaw E, O'Sullivan D, Poirier AE, Heer E, Villeneuve PJ, Walter SD, Friedenreich CM, Smith L, De P. Age-standardized cancer-incidence trends in Canada, 1971–2015. CMAJ. 2019;191(46):E1262–73. https://doi.org/10.1503/cmaj.190355.
10. Castañeda-Avila M, Torres-Cintrón CR, Cruz-Benítez A, Fuentes-Payán W, Maldonado-Albertorio A, Nieves-Ferrer L, Padró-Juarbe P, Soto-Abreu R, Perez-Ríos N, Ortiz-Ortiz KJ, Magno P, Ortiz AP. Pancreatic cancer incidence, mortality, and survival in Puerto Rico, 2001–2015. P R Health Sci J. 2019;38(3):148–55.
11. Blackford AL, Canto MI, Klein AP, Hruban RH, Goggins M. Recent trends in the incidence and survival of Stage 1A pancreatic cancer: a surveillance, epidemiology, and end results analysis. J Natl Cancer Inst. 2020; https://doi.org/10.1093/jnci/djaa004. [Epub ahead of print].
12. European Commission. European cancer information system. 2018. https://ecis.jrc.ec.europa.eu/explorer.php?$1-AE28$2-All$4-1,2$3-All$6-0,14$5-2008,2008$7-7$0-0$CEstByCancer$X0_8-3$CEstRelativeCanc$X1_8-3$X1_9-AE28.
13. The Global Cancer Observatory. The Netherlands 2018. 528 – the-netherlands-fact-sheets.pdf. Retrieved from gco.iarc.fr.
14. Hurton S, MacDonald F, Porter G, Walsh M, Molinari M. The current state of pancreatic cancer in Canada: incidence, mortality, and surgical therapy. Pancreas. 2014;43(6):879–85.
15. National Cancer Institute. 2020. https://seer.cancer.gov/statfacts/html/pancreas.html.

Chapter 3
Hereditary Syndromes and Pancreatic Cancer

Laura Pölsler, Kathleen B. M. Claes, and Johannes Zschocke

Take Home Messages

- Known genetic risk factors for pancreatic cancer include germline pathogenic variants in *STK11*, *CDKN2A*, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *APC*, and *TP53*.
- Known genetic tumour predisposition syndromes explain up to 15% of familial aggregation of pancreatic cancer.
- Surveillance in high-risk constellations has been recommended
  - for first degree relatives from familial pancreatic cancer kindreds (i.e. ≥ 2 patients with pancreatic cancer who are first degree relatives or ≥3 patients with pancreatic cancer in one family).
  - for mutation carriers of known genetic tumour predisposition syndromes.
- Details of these recommendations require further evaluation within clinical trials.

Pearls and Pitfalls

- To diagnose hereditary tumour predisposition syndromes, massive parallel sequencing (next generation sequencing, NGS) in an affected patient is the method of choice.

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- The identification of large deletions or duplications with this method requires special analysis strategies that may not be available in all laboratories (enquire about alternatives).
- cDNA sequencing may need to be employed to detect (deep) intronic mutations that cause splicing effects.
- For predictive testing in a healthy family member a causal germline mutation in an index patient with pancreatic cancer should have been identified.

Future Perspectives
- Technical advances will improve genetic testing techniques for reliable testing of DNA from all tissues, including paraffin-embedded tumour tissue.
- Knowledge of known and new tumour predisposition syndromes should help to understand tumour risk differences within and between families.

3.1 Introduction

As described in Chap. 4, up to 10% of patients with pancreatic cancer have a positive family history with at least one relative who is also affected [1–3]. While the reasons for most familial aggregation remain to be elucidated, pancreatic cancer can occur as part of specific tumour predisposition syndromes, which are usually dominated by other cancers. An increased pancreatic cancer risk is also associated with hereditary diseases, such as *PRSS1*-related or *CFTR*-associated hereditary pancreatitis. Finally, genome-wide association studies indicated that a number of common genetic variants are associated with increased pancreatic cancer risk. Although this risk is quite small for the individual variant, the collective influence may be quite relevant [4, 5].

In this review, we will discuss genetic causes of increased pancreatic cancer risk. We only include pancreatic ductal adenocarcinoma (PDAC) which accounts for more than 95% of pancreatic cancers. Other pancreatic neoplasia, such as neuroendocrine tumours of the pancreas (PNETs), which has an increased prevalence in some hereditary diseases, such as multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), or Von Hippel Lindau (VHL) syndrome, is not covered [6].

3.2 Hereditary Tumour Predisposition Syndromes

Pathogenic variants in genes associated with known hereditary tumour predisposition syndromes are found in 3–9% of pancreatic cancer patients unselected for family history and 8–15% of familial pancreatic cancer kindreds (Table 3.1). There is a wide range of causative genes, and there is no known single gene responsible for the majority of familial pancreatic cancer families. Below we provide an overview of the major syndromes with a genetic susceptibility for pancreatic cancer. Interestingly,

Table 3.1 Probability of finding pathogenic variants in one of the genes causing a known hereditary tumour predisposition syndrome in pancreatic cancer patients according to family history

	Number of patients	PC patients unselected for FH	PC patients with some FH for PC	PC patients from FPC kindreds
Hu et al. 2016 [8]	96	9.4%		
Shindo et al. 2017 [9]	854	3.5%		
Young et al. 2018 [10]	274	4.7%		
Yurgelun et al. 2019 [11]	289	6.6%		
Hu et al. 2018 [12]	3030 PC, 343 some FH	6.2%	9.6%	
Salo-Mullen et al. 2015 [13]	195 PC, 34 FPC	15.1%[a]		5.9%[a]
Zhen et al. 2015 [14]	515 FPC, 201 some FH		3.5%[b]	8%[b]
Chaffee et al. 2018 [15]	185 FPC, 117 some FH		4.3%	11.9%
Schwartz et al. 2019 [16]	133 FPC, 84 some FH		4.6%	8.3%
Takai et al. 2016 [17]	54 FPC			14.5%
Roberts et al. 2016 [18]	593 FPC			11.3%
Lener et al. 2017 [19]	398 FPC			2%[c]

Results shown are restricted to likely pathogenic/pathogenic variants in genes that have a confirmed association with pancreatic cancer, including *TP53* and *APC*

FH family history, *FPC* Familial pancreatic cancer, *PC* pancreatic cancer

[a]This study had a high proportion of patients with Ashkenazi ancestry (60.4%)

[b]This study only tested the genes *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A*

[c]This study only tested certain founder mutations in the Polish population in the genes *BRCA1*, *PALB2*, *CHEK2*, and *NBS1*

several of the pancreatic cancer predisposition genes are mutated somatically in tumours—*CDKN2A* is amongst the five most frequently mutated genes in pancreatic cancer. Also, mutations in *STK11* are regularly observed [7].

The majority of the genes involved are tumour suppressor genes. In accordance with the "two-hit-hypothesis" of Alfred Knudson [20], tumours develop if both copies of such a gene have been inactivated. In familial cases one mutated copy has been inherited and is present in all cells (i.e. a germline mutation), making it much more likely that a second (somatic) hit completely abolishes gene function. Most tumour predisposition syndromes follow an autosomal dominant inheritance pattern. Children of mutation carriers inherit the gene copy with the mutation with a probability of 50%, irrespective of the gender of the carrier parent or the child. The magnitude of the specific cancer risks, on the other hand, can be gender-specific, depending on the gene and organ site involved. The recurrence risk (for the cancer risk predisposition) in these diseases is therefore 50%.

Familial pancreatic cancer outside of known tumour disposition syndromes represents a heterogeneous group of risk constellations caused by variation in numerous genes in a polygenic or multifactorial fashion.

3.2.1 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare tumour predisposition syndrome; its exact incidence has not yet been clarified, but estimates range from 1 in 200,000 to 1 in 50,000 [21]. PJS is caused by heterozygous loss-of-function mutations in the *STK11* (serine/threonine kinase 11) gene (OMIM *602216, formerly *LKB1*) on chromosome 19 and is inherited in an autosomal dominant manner.

The STK11 enzyme phosphorylates and activates AMP-activated protein kinase (AMPK), which negatively regulates cancer cell proliferation and metabolism by promoting apoptosis. The STK11/AMPK pathway is also involved in the process of tumour invasion and migration. Loss of STK11 is associated with increased expression of NADPH oxidase 1 (NOX1), which promotes the angiogenic switch by increasing redox oxygen species (ROS) generation and expression of vascular endothelial factor (VEGF). STK11 also has a role in regulation of cell polarity and epithelial integrity across species [22]. This means that it helps certain types of cells to orientate themselves correctly within tissues.

PJS is characterized by a specific form of gastrointestinal hamartomatous polyposis, consisting of so-called Peutz-Jeghers-type polyps. These occur predominantly in the small intestine and at a lesser frequency in the stomach and the large intestine, but also at other extra-intestinal sites, such as the nasal and bronchial mucous membranes, the gall bladder, or the bladder and ureters. Perioral, perinasal, and perianal mucocutaneous hyperpigmented maculae are an additional feature of PJS that is detectable in most patients and more pronounced during childhood [23, 24]. Additionally, PJS confers an increased risk for malign and benign tumour formation in diverse organs, including pancreatic cancer, breast cancer, intestinal cancers, and a signature gynaecological neoplasm, the minimal deviation adenocarcinoma of the cervix [23]. Benign tumours include large calcifying Sertoli cell tumours of the testes or sex cord tumours with annular tubules of the ovaries (SCTAT), both of which have an elevated risk of becoming malignant [25].

The (clinical) diagnosis of PJS is established in a patient with two or more histologically confirmed PJS-type hamartomatous polyps, when a PJS-type polyp *or* the characteristic mucocutaneous pigmentation occur in an individual who has a family history of PJS, or in a patient with both a PJS-type polyp *and* the typical mucocutaneous pigmentation [23]. It should be noted that this pigmentation may fade away during puberty/adulthood. Other authors included identification of a heterozygous pathogenic variant in *STK11* by molecular genetic testing as another diagnostic

criterion [26]. Approximately 95% of patients with a clinical diagnosis of PJS show a mutation in *STK11* [27, 28]. Conversely, *STK11* mutations are not usually identified in familial pancreatic cancer without clinical PJS criteria or patients with sporadic pancreatic cancer or premalignant lesions [9, 12, 15, 18, 29, 30], concluding that PJS is a rare cause for familial aggregation of pancreatic cancer.

Patients with PJS have increased lifetime risks for colorectal, breast, and gastric cancer (>25%), for small bowel, ovarian, and cervical cancer (15–25%), and for uterine, testicular, and lung cancer (<15%) [28, 31–33]. The pancreatic cancer risk is highly elevated and has been estimated between 11 and 55% up to the age of 75 years [27, 31–33]. This corresponds to a 76–140-fold relative risk compared to the general population [27, 31, 33].

Recommendations therefore include pancreatic cancer surveillance in any patient with proven Peutz-Jeghers syndrome, irrespective of family history [34].

3.2.2 Familial Atypical Multiple Mole Melanoma and Pancreatic Cancer Syndrome (FAMMM)

Familial atypical multiple mole melanoma syndrome (FAMMM) was first described by Lynch and Krush in 1968 [35]. It is caused by deleterious variants in *CDKN2A* and was first identified as a cause for melanoma aggregation in 1994 [36]. The gene codes for p16(Ink4a) and for the alternate reading frame protein product, p14ARF [37]. Both p16(Ink4a) and p14ARF are involved in cellular senescence. Furthermore, p16(Ink4a) is a cell cycle inhibitor by binding to CDK4 and CDK6. Hereby, phosphorylation of the retinoblastoma protein is inhibited, forcing cells to remain in the G1 phase and therefore arresting cell division [38].

The clinical picture in FAMMM include (a) multiple, atypical melanocytic naevi as well as a high total body naevi count with particular histologic features and (b) a cutaneous melanoma in at least one first or second degree relative [39]. Affected individuals also have a strongly increased risk for pancreatic cancer. Of families with three related melanoma patients, approximately 30% had *CDKN2A* mutations (fewer in Australia, more in Europe; [37]).

CDKN2A mutations have also been identified in patients with pancreatic cancer without family history of melanoma [14, 40, 41]. In familial pancreatic cancer, *CDKN2A* mutations have been reported in 2.2–3.3% of families [14, 15, 42, 43]. *CDKN2A* mutations are uncommon in patients with pancreatic cancer unselected for family history of any cancer [9, 12, 43].

In patients with *CDKN2A* mutations the lifetime risk for malignant melanoma (to the age of 80 years) has been reported as 45–67% in family-based [44, 45] and below 30% in population-based cohorts [46, 47]. The risk for pancreatic cancer has been estimated as 17% up to the age of 75 years [48]. Individuals with a *CDKN2A* mutation should therefore also undergo screening for pancreatic cancer [34].

3.2.3 Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is caused by mutations in either *BRCA1* on chromosome 17 or *BRCA2* on chromosome 13. It is inherited in an autosomal dominant manner and leads to an increased cancer risk, especially for breast and/or ovarian cancer in women.

BRCA1 and BRCA2 are involved in the maintenance of genome stability. They are both involved in repair of DNA double strand breaks by homologous recombination [49]. However, the two proteins work at different stages in the DNA damage response (DDR) and in DNA repair. BRCA1 is a pleiotropic DDR protein that functions in both checkpoint activation and DNA repair (including regulation of transcription). BRCA2 is a mediator of the core mechanism of homologous recombination by mediating the recruitment of the recombinase RAD51 to DNA double strand breaks [50].

Genetic testing of *BRCA1* and *BRCA2* has been recommended in high-risk situations: details vary from country to country but include a personal and/or family history of early onset breast cancer, multiple cases of (premenopausal) breast or ovarian cancer, and combinations of breast and ovarian cancer, as well as certain immunohistological breast cancer subtypes (triple negative breast cancer). Recommendations for affected women include close interval breast tissue screening via MRI as well as sonography and mammography from age 20–25. Risk-reducing surgery for breast (risk reducing mastectomy) and ovarian tissue (risk reducing salpingoophorectomy) strongly reduces cancer burden [51]. Also, platinum based chemotherapy and targeted tumour therapy with PARP inhibitors have shown particular effectiveness in BRCA-related cancers [52], including pancreatic cancer [53].

The cumulative risk for breast and ovarian cancer, respectively, has been estimated at 55 and 39% in *BRCA1* mutation carriers, and 47 and 19% in *BRCA2* mutation carriers [54]. There is also an increased risk for colon cancer, melanoma skin cancer, and prostate cancer [55–59], as well as pancreatic cancer. Pancreatic cancer risk appears to be somewhat higher in individuals with *BRCA2* mutation, compared to *BRCA1* mutations: the relative risk (RR) for pancreatic cancer compared to the general population has been reported as 2–6 for persons with *BRCA2* mutations, and 2–5 for persons with *BRCA1* mutations (Table 3.2).

BRCA1 and *BRCA2* mutations account for 1–1.5% and 3–7%, respectively, of familial pancreatic cancer cases, and <1% and 1.4–4%, respectively, in patients with pancreatic cancer unselected for family history (Table 3.2). Mutations in *BRCA2* are thus amongst the most common high-risk monogenic risk factors for pancreatic cancer. Pancreatic cancer surveillance has been suggested in patients with *BRCA1* and *BRCA2* mutations who have a first-degree relative with pancreatic cancer [34].

Table 3.2 Probability of finding a pathogenic variant in *BRCA1* or *BRCA2* in pancreatic cancer patients according to family history

	Number of patients	PC patients unselected for FH		PC patients with some FH for PC		PC patients from FPC kindreds	
		BRCA1	*BRCA2*	*BRCA1*	*BRCA2*	*BRCA1*	*BRCA2*
Goggins et al. 1996 [60]	41		7.3%[a]				
Holter et al. 2015 [61]	306	1%[b]	3.6%[b]				
Waddell et al. 2015 [62]	100	None	4%				
Shindo et al. 2017 [9]	854	0.35%	1.4%				
Hu et al. 2016 [8]	96	1.1%	2.1%				
Young et al. 2018 [10]	274	0.4%	1.1%				
Yurgelun et al. 2019 [11]	289	1%	1.4%				
Hu et al. 2018 [12]	3030 PC, 343 some FH	0.6%	1.9%	0.6%	2%		
Salo-Mullen et al. 2015 [13]	159 PC, 34 FPC	2.5%[b]	8.2%[b]			3.9%[b]	3.9%[b]
Zhen et al. 2015 [14]	515 FPC, 201 some FH			None	3%	1.2%	3.7%
Chaffee et al. 2018 [15]	185 FPC, 117 some FH			None	2.6%[c]	1.1%	4.3%
Couch et al. 2007 [63]	180 FPC						5.6%[a]
Slater et al. 2010 [64]	70 FPC						2.8%[d]
Roberts et al. 2016 [18]	593 FPC					1.2%	1.7%
Takai et al. 2016 [17]	54 FPC					None	5.6%
Lener et al. 2017 [19]	398 FPC					1.3%[e]	1.3%[e]

FH family history, *FPC* Familial pancreatic cancer, *PC* pancreatic cancer

[a]This study only tested the *BRCA2* gene

[b]This study had a high proportion of patients with Ashkenazi ancestry (10.8% [61], 60.4% [13])

[c]Non-familial cases

[d]This study only tested the genes *BRCA2* and *CDKN2A*

[e]This study only tested certain founder mutations in the Polish population in the genes *BRCA1*, *PALB2*, *CHEK2*, and *NBS1*

3.2.4 PALB2 *Gene Mutations*

PALB2 is firmly established as a bona fide breast cancer risk gene. Its protein product serves as the molecular scaffold in the formation of the BRCA1-PALB2-BRCA2 complex, which is essential for homologous recombination (HR). Via its WD repeats it is proposed to scaffold a HR complex containing RAD51C and BRCA2, which has an important role in HR-mediated DNA repair [65].

PALB2 germline mutations confer an estimated life time risk for breast cancer of about 40–55% in women without a significant breast cancer family, and >75% in those with more than one first degree relative with breast cancer [66, 67]. Mutations in *PALB2* were also correlated with an increased risk for other cancers, such as ovarian cancer and male breast cancer [67], and were discussed to cause an increased risk for gastric cancer [68]. Recent studies showed a moderately increased risk for pancreatic cancer in a large cohort of patients with *PALB2* mutations: the relative risk was calculated as 2.37 (95% confidence interval, 1.24–4.50), reflecting an absolute risk of developing pancreatic cancer by the age of 80 years of 2–3% [67]. *PALB2* mutations have been found in 0.3–3% of patients with pancreatic cancer unselected for family history and 0.5–3.7% of familial pancreatic cancer families [9, 11, 12, 14, 15, 17, 62, 69–72].

Surveillance for pancreatic cancer has been suggested for patients with *PALB2* mutations if there was pancreatic cancer in a first-degree relative [34].

3.2.5 ATM *Gene Mutations*

ATM is a serine/threonine protein kinase, which activates checkpoint signaling upon double strand breaks, apoptosis, and genotoxic stresses, thereby acting as a DNA damage sensor, leading to cell cycle arrest, DNA repair, or apoptosis. *BRCA1* is one of its target genes, as well as *TP53* and *CHEK2* [73].

Biallelic germline mutations in *ATM* are known to cause Ataxia telangiectasia, a rare disease characterized by progressive ataxia in childhood, conjunctival telangiectasias, and an increased risk for cancer, especially leukemias and lymphomas [74]. Heterozygous *ATM* mutations were associated with a milder increase in cancer risk: while a moderate increase in female breast cancer risk in *ATM* mutation carriers is well recognized (relative risk 2.8 [75]) and varies with family history and, possibly, mutation type (missense versus truncating mutations)[76], pancreatic cancer risk has not been well established. A meta-analysis of the sparse data showed a relative risk for pancreatic cancer of about 2.2 [77]. Heterozygous *ATM* (mainly truncating) mutations are found in about 1–2.3% of pancreatic cancer patients unselected for family history or 2.4–4% of patients from familial pancreatic cancer kindreds [11, 12, 15, 17, 78].

Increased risk surveillance strategies for pancreatic cancer are recommended in heterozygous (truncating) *ATM* mutation carriers in case a first-degree relative had pancreatic cancer [34].

3.2.6 Lynch Syndrome

Lynch syndrome (formerly hereditary non-polyposis colorectal cancer, HNPCC) is caused by heterozygous mutations in the genes coding for DNA mismatch repair (MMR) proteins, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. There is also a recurrent large deletion involving the *EPCAM* gene that causes *MSH2* silencing. Lynch syndrome is inherited in an autosomal dominant manner and leads to increased cancer risks, especially colorectal cancer, as well as endometrial and ovarian cancer in women [79]. Cancers associated with Lynch syndrome show loss of function of the MMR system characterized by high microsatellite instability (MSI-high) [80]. Lynch syndrome causes about 3% of colorectal cancers [81] and 2–4% of endometrial cancers. Previously, clinical and histopathological criteria (Amsterdam II criteria and revised Bethesda criteria) were used to identify individuals with an increased likelihood of Lynch syndrome. However, because of novel targeted therapies for MSI-high tumours [82] and reduced costs of mutation analysis, newer recommendations suggest reflexive genetic testing [81].

Lynch syndrome due to *MLH1* mutations confers a relative risk of 7.8 for pancreatic cancer [83]. The life-time cumulative risks for extra-colonic intestinal cancers (including stomach, pancreas, small bowel, bile duct, and gall bladder) in women and men, respectively, were reported as 11 and 21% for *MLH1* mutations, 13 and 20% for *MSH2* mutations, 4 and 8% for *MSH6* mutations, and 4% (both sexes) for *PMS2* mutations [84]. *MLH1*, *MSH2*, *MSH6* or *PMS2* mutations account for 1–2% of familial pancreatic cancer cases [15, 17] and were found in 0.2–1% of patients with pancreatic cancer unselected for family history [9, 11, 12].

Pancreatic cancer surveillance has been suggested for individuals with *MLH1, MSH2* or *MSH6* mutations who have at least one first degree relative with pancreatic cancer [34].

3.3 Hereditary Pancreatitis

Chronic pancreatitis is a known risk factor for pancreatic carcinoma but the magnitude of this risk is unclear. While most cases of chronic pancreatitis are attributed to unfavourable lifestyle and environmental factors, mutations in a number of genes have been linked to an increased risk of pancreatitis [85]. Genes reported to be associated with hereditary pancreatitis include *PRSS1*, *CFTR*, *SPINK1*,

CTRC [86], *CPA1*, and *CPB1* [87]. In a recent meta-analysis, overall long term effect estimates (over 9 years lag period between diagnosis of chronic pancreatitis and pancreatic cancer) were 3.55-fold increased in comparison to the general population and remained elevated when corrected for known environmental risk factors such as smoking [88]. High-risk pancreatic cancer surveillance is recommended in patients with hereditary pancreatitis irrespective of gene mutation status and should start at the age of 40 or 20 years after the first pancreatitis attack [34].

3.4 Other Tumour Predisposition Syndromes

3.4.1 Li Fraumeni Syndrome

Li Fraumeni syndrome (LFS) caused by heterozygous mutations in *TP53* is associated with highly increased risks for cancer in a wide range of organs and tissues, including childhood cancers such as adrenocortical carcinoma, osteosarcoma and soft tissue sarcoma, brain tumours, leukemias and lymphomas, and premenopausal breast cancer [89]. Pancreatic cancer is one of the cancer reported in LFS patients in older age [89, 90]. The relative risk for pancreatic cancer in LFS has been calculated to be 7.3 [91]. *TP53* mutations have not been included in surveillance guidelines for persons with high pancreatic cancer risk [34], but LFS specific cancer surveillance recommendations exist [92].

3.4.2 Familial Adenomatous Polyposis

Pancreatic cancer is rarely found in familial adenomatous polyposis (FAP), a hereditary tumour predisposition syndrome characterized by numerous adenomatous polyps. FAP is caused by heterozygous mutations in the *APC* gene, and in its classical form invariably leads to colorectal cancer by the age of 40 years [93]. It is unclear whether FAP is associated with an increased pancreatic cancer risk. One cohort study of FAP patients calculated a relative risk of 4.5 (95% confidence limits 1.2–11.4) for pancreatic cancer compared to the general population [94], but data are scarce [95]. *APC* mutations have not been included in surveillance recommendations for persons with high pancreatic cancer risk [34].

3.4.3 Germline Mutations in Other Cancer Genes

Germline mutations in other cancer genes such as *CHEK2, CDH1, BRIP1, RAD50, RAD51C, RAD51D, TET2, ASXL1,* or *PALLD* or monoallelic mutations in *FANCA, FANCC, FANCG,* or *MUTYH* [9, 11, 12, 18, 96] have been described in pancreatic cancer cases, but firm associations have not (yet) been established. A recent report of a heterozygous *RABL3* nonsense mutation segregating with an extensive cancer phenotype including five pancreatic cancers in one large family, as well as functional analyses, suggested a potential connection of *RABL3* with pancreatic cancer development through the RAS pathway [97].

3.5 Testing and Tools

When a genetic tumour predisposition syndrome is suspected in a patient with pancreatic cancer, finding the causal germline mutation is of high relevance for the management of the patient, including the design of targeted therapy (if available), the estimation of cancer recurrence risk, and the application of appropriate surveillance measures. Additionally, identifying the causal germline mutation in an affected index patient enables predictive testing of healthy family members who might also at increased risk of developing cancer. A decision flow is depicted in Fig. 3.1.

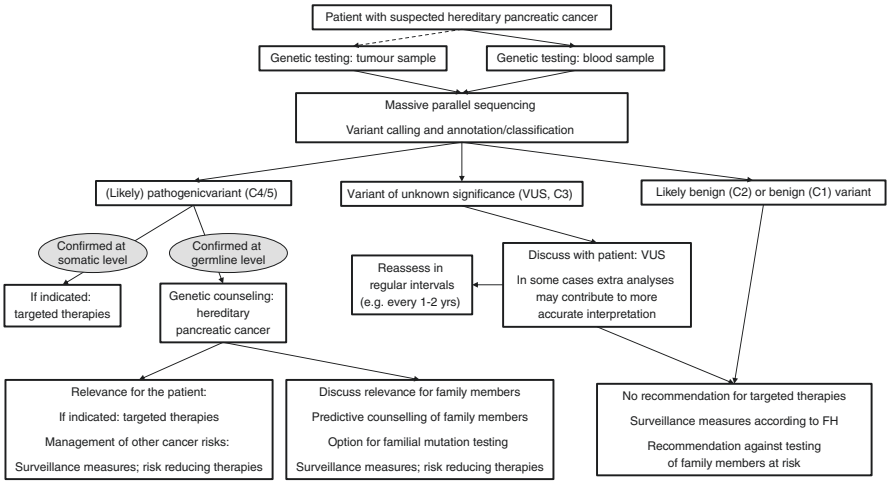

Fig. 3.1 Decision flow in germline genetic testing. Blood sample can be replaced by buccal swap or urine sample (unaffected tissue). Consider false negative results due to technical limitations of tumour testing, especially from paraffin-embedded samples. Classification of variants in five classes according to guidelines of the American College of Medical Genetics (ACMG; [98]). *C* variation class according to ACMG, *FH* family history, *VUS* variant of unknown significance

Diagnostic molecular genetic testing in a cancer patient is best performed by massive parallel sequencing of all relevant genes using DNA isolated from lymphocytes from a sample of the patient's peripheral blood. However, in order to facilitate clear interpretation of the test results, analysis of individual syndromes should be limited to those conditions that are compatible with the clinical presentation and family history. When ordering genetic testing in a genetic laboratory, it is essential to provide information about personal and family history.

Detected variants are classified into one of five classes (C1–C5) according to the guidelines of the American College of Medical Genetics (ACMG) [98] (Fig. 3.1), whereby C4 (likely pathogenic) and C5 (pathogenic) variants are clinically most relevant, confirming the diagnosis of a genetic tumour predisposition syndrome. This allows for targeted testing (usually by Sanger sequencing) in healthy (predictive testing) or affected (diagnostic testing) family members. If it concerns a highly penetrant tumour predisposition syndrome, the same causal mutation (usually) segregates in a given family. In rare cases, the tumour predisposition syndrome is caused by a so-called "de novo" mutation, meaning that it arose anew in the germline of the patient with cancer. Then, only descendants of the patient will be at risk of inheriting the mutation. The interpretation of findings of germline genetic analyses is difficult in cases where unaffected family members are tested without a proven causal germline mutation in an affected member. Additionally, caution is warranted for those pathogenic mutations that do not confer a traditional risk profile but cause reduced risk elevation (termed "hypomorphic mutations") in comparison with classical pathogenic mutations within the gene.

Normal variation within the gene (i.e. variation that is found in the normal healthy population) is usually not reported (C1 = benign and C2 = likely benign variation). A "normal result" (no pathological findings) in a pancreatic cancer patient may indicate either (a) there actually is no pathogenic germline mutation in the genes tested, or (b) there *is* a pathogenic germline mutation that is not detected by the method employed. Mutations that may be missed include (deep) intronic variants, variants in regulatory elements of the gene, or large deletions/duplications if they are not covered by the test. In this case, other techniques may elucidate the pathogenic mechanism of some of these mutations. Multiplex ligation probe amplification testing can demonstrate deletion or duplication of one or more exons of a given gene. cDNA sequencing can show a splice effect caused by an intronic mutation not recognized by exon-based approaches.

The third outcome of genetic germline testing is the identification of variants of unknown significance (VUS; C3). These are variants for which only limited or conflicting data exist and which therefore cannot be interpreted conclusively at the time of reporting. They are a well-recognized source of uncertainty in genomic medicine and may induce anxiety and erroneous interpretations in some patients. Segregation testing in other affected family members can reduce the likelihood of causality but co-segregation should not be regarded as proof of pathogenicity. Loss of heterozygosity (i.e. loss of the wild-type allele) in the tumour may support a possible causal role. However, definite conclusions on pathogenicity based on findings in a single family are usually *not* possible.

DNA isolated from tumour tissue can be used to perform genetic testing but is still constrained by technical limitations. Germline mutations that are identified when sequencing DNA extracted from peripheral blood can usually also be detected in tumour samples although this is not always the case, particularly when the tumour DNA is derived from paraffin-embedded tissue. The presence of somatic mutations (limited to the tumour tissue) can confound interpretation as it is usually not easily possible to distinguish germline from somatic variants in tumour tissue based on sequencing data. Our recommended approach is to inquire and make a complete family history and discuss cases with the Medical Genetics team whenever the diagnostic route or results are unclear.

3.6 Surveillance/Screening Recommendations

A recent consensus statement of The International Cancer of the Pancreas Screening (CAPS) Consortium outlined details with regard to surveillance of persons at risk for pancreatic cancer from tumour predispositions syndromes or familial pancreatic cancer families. Consensus was reached that surveillance should include high-risk patients; the aim of surveillance is to detect and treat stage I pancreatic cancer and pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN) [34]. Details on surveillance are provided in Table 3.3. For surveillance, endoscopic ultrasound and MRI/magnetic retrograde cholangiopancreatography are preferred, but no consensus was reached on how to alternate these modalities.

Table 3.3 Recommendations for pancreatic cancer surveillance in high-risk individuals

Gene/risk constellation	Irrespective of FH	If ≥1 FDR with PC	Age at start of surveillance[a]	Other cancer surveillance recommendations
STK11/Peutz Jeghers syndrome	X		40 yrs	• Yearly from 25 yrs: breast MRI and/or mammogram, pelvic exam and pelvic/transvaginal ultrasound, PAP smear • Every 3 yrs: lower and upper endoscopy, incl. video capsule endoscopy, starting at 8 yrs/18 yrs
CDKN2A	X		40 yrs	• Every 3–6 mo: dermoscopic examination • Every 6 mo: total body photography
BRCA1 and *BRCA2*		X	45 or 50 yrs	• Every 6–12 mo from 20 to 25 yrs: breast MRI, sonography, and/or mammography • Offer RRM and RRSO • Consider colonoscopy according to FH

(continued)

Table 3.3 (continued)

Gene/risk constellation	Irrespective of FH	If ≥1 FDR with PC	Age at start of surveillance[a]	Other cancer surveillance recommendations
PALB2		X	45 or 50 yrs	• Yearly from 30 yrs: breast MRI and/or mammography • Consider colonoscopy and RRSO according to FH
ATM		X	45 or 50 yrs	• Yearly from 40 yrs (35 yrs, if clear FH of BC): breast MRI and/or mammography • Consider colonoscopy and RRSO according to FH
MLH1, *MSH2*, *MSH6*		X	45 or 50 yrs	• Close interval colonoscopies from 25 yrs • Sonographic surveillance for endometrial cancer, consider RRH and RRSO • Regular upper gastrointestinal tract endoscopy and control of helicobacter infection • Screening for urinary tract cancers in *MSH2* mutation carriers • Chemoprophylaxis with acetylsalicylic acid
FDR of a patient from a FPC kindred[b]			50 or 55 yrs	
Onset of diabetes in any of the above	X		At diagnosis	

General measures: baseline imaging including magnetic resonance imaging/magnetic retrograde cholangiopancreatography (MRI/MRCP) and endoscopic ultrasound (EUS); fasting blood glucose and/or hemoglobin A1c

Follow-up surveillance: yearly MRI/MRCP and EUS (possibly alternating) with regular control of fasting blood glucose and/or HbA1c

Recommendations according to Goggins et al. 2020 [34]

FH family history, *FDR* first degree relative, *PC* pancreatic cancer, *FPC* familial pancreatic cancer, *mo* months, *yrs* years, *RRM* risk reducing mastectomy, *RRSO* risk reducing salpingo-oophorectomy, *RRH* risk reducing hysterectomy

[a]If 10 years younger than the youngest affected in the family is before recommended starting age, start at earlier age

[b]A FPC kindred is defined as a family with two first-degree relatives with PC or with three relatives with PC

In case of highly suspicious lesions (e.g. large solid lesions, solid lesions with main pancreatic duct strictures, symptomatic cystic lesions, or lesions with thickened walls or solid components), oncological radical resection should be performed at a specialized centre. Unclear lesions with a low probability of malignancy should be reviewed after 3–6 months [34].

However, firm and proven protocols for pancreatic surveillance are yet to be established for high-risk individuals. Until more evidence supporting the CAPS recommendations is available, they should be performed in a research setting by multidisciplinary teams in centres with appropriate expertise. The benefits, risks, and costs of surveillance definitively need additional evaluation.

3.7 Conclusion

Pancreatic cancer aggegration in families is due to a known genetic tumour predisposition syndrome in about 15% of families and includes heterozygous pathogenic variants in the genes *STK11*, *CDKN2A*, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *APC*, and *TP53*. Increased pancreatic cancer risk has yet to be proven unequivocally for other candidate genes. For most of the known tumour predisposition syndromes, the specific cancer risk profile includes other cancers in addition to pancreatic cancer. This must be considered when cancer surveillance is recommended. High-risk pancreatic cancer surveillance protocols have been published but their benefit has yet to be corroborated by clinical trials.

References

1. Duffy A, Capanu M, Allen P, Kurtz R, Olson SH, Ludwig E, et al. Pancreatic adenocarcinoma in a young patient population—12-year experience at Memorial Sloan Kettering Cancer Center. J Surg Oncol. 2009;100(1):8–12. https://doi.org/10.1002/jso.21292.
2. Lin JC, Chan DC, Chen PJ, Chu HC, Chueh TH, Huang HH, et al. Clinical characteristics of early onset pancreatic adenocarcinoma: a medical center experience and review of the literature. Pancreas. 2011;40(4):638–9. https://doi.org/10.1097/MPA.0b013e318214fe56.
3. McWilliams RR, Maisonneuve P, Bamlet WR, Petersen GM, Li D, Risch HA, et al. Risk factors for early-onset and very-early-onset pancreatic adenocarcinoma: a Pancreatic Cancer Case-Control Consortium (PanC4) analysis. Pancreas. 2016;45(2):311–6. https://doi.org/10.1097/MPA.0000000000000392.
4. Chen F, Childs EJ, Mocci E, Bracci P, Gallinger S, Li D, et al. Analysis of heritability and genetic architecture of pancreatic cancer: a PanC4 study. Cancer Epidemiol Biomarkers Prev. 2019;28(7):1238–45. https://doi.org/10.1158/1055-9965.EPI-18-1235.
5. Childs EJ, Mocci E, Campa D, Bracci PM, Gallinger S, Goggins M, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. Nat Genet. 2015;47(8):911–6. https://doi.org/10.1038/ng.3341.
6. Pea A, Hruban RH, Wood LD. Genetics of pancreatic neuroendocrine tumors: implications for the clinic. Expert Rev Gastroenterol Hepatol. 2015;9(11):1407–19. https://doi.org/10.1586/17474124.2015.1092383.
7. Heestand GM, Kurzrock R. Molecular landscape of pancreatic cancer: implications for current clinical trials. Oncotarget. 2015;6(7):4553–61. https://doi.org/10.18632/oncotarget.2972.
8. Hu C, Hart SN, Bamlet WR, Moore RM, Nandakumar K, Eckloff BW, et al. Prevalence of pathogenic mutations in cancer predisposition genes among pancreatic cancer patients. Cancer Epidemiol Biomarkers Prev. 2016;25(1):207–11. https://doi.org/10.1158/1055-9965.EPI-15-0455.

9. Shindo K, Yu J, Suenaga M, Fesharakizadeh S, Cho C, Macgregor-Das A, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol. 2017;35(30):3382–90. https://doi.org/10.1200/JCO.2017.72.3502.
10. Young EL, Thompson BA, Neklason DW, Firpo MA, Werner T, Bell R, et al. Pancreatic cancer as a sentinel for hereditary cancer predisposition. BMC Cancer. 2018;18(1):697. https://doi.org/10.1186/s12885-018-4573-5.
11. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, Rubinson DA, Dunne RF, Kozak MM, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21(1):213–23. https://doi.org/10.1038/s41436-018-0009-5.
12. Hu C, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA. 2018;319(23):2401–9. https://doi.org/10.1001/jama.2018.6228.
13. Salo-Mullen EE, O'Reilly EM, Kelsen DP, Ashraf AM, Lowery MA, Yu KH, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015;121(24):4382–8. https://doi.org/10.1002/cncr.29664.
14. Zhen DB, Rabe KG, Gallinger S, Syngal S, Schwartz AG, Goggins MG, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. Genet Med. 2015;17(7):569–77. https://doi.org/10.1038/gim.2014.153.
15. Chaffee KG, Oberg AL, McWilliams RR, Majithia N, Allen BA, Kidd J, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. Genet Med. 2018;20(1):119–27. https://doi.org/10.1038/gim.2017.85.
16. Schwartz M, Korenbaum C, Benfoda M, Mary M, Colas C, Coulet F, et al. Familial pancreatic adenocarcinoma: a retrospective analysis of germline genetic testing in a French multicentre cohort. Clin Genet. 2019;96(6):579–84. https://doi.org/10.1111/cge.13629.
17. Takai E, Yachida S, Shimizu K, Furuse J, Kubo E, Ohmoto A, et al. Germline mutations in Japanese familial pancreatic cancer patients. Oncotarget. 2016;7(45):74227–35. https://doi.org/10.18632/oncotarget.12490.
18. Roberts NJ, Norris AL, Petersen GM, Bondy ML, Brand R, Gallinger S, et al. Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov. 2016;6(2):166–75. https://doi.org/10.1158/2159-8290.CD-15-0402.
19. Lener MR, Kashyap A, Kluzniak W, Cybulski C, Soluch A, Pietrzak S, et al. The prevalence of founder mutations among individuals from families with familial pancreatic cancer syndrome. Cancer Res Treat. 2017;49(2):430–6. https://doi.org/10.4143/crt.2016.217.
20. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971;68(4):820–3. https://doi.org/10.1073/pnas.68.4.820.
21. Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol. 2006;4(4):408–15. https://doi.org/10.1016/j.cgh.2005.11.005.
22. Martin-Belmonte F, Perez-Moreno M. Epithelial cell polarity, stem cells and cancer. Nat Rev Cancer. 2011;12(1):23–38. https://doi.org/10.1038/nrc3169.
23. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut. 2010;59(7):975–86. https://doi.org/10.1136/gut.2009.198499.
24. Jeghers H, Mc KV, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. N Engl J Med. 1949;241(25):993, illust; passim. https://doi.org/10.1056/NEJM194912222412501.
25. Ulbright TM, Amin MB, Young RH. Intratubular large cell hyalinizing sertoli cell neoplasia of the testis: a report of 8 cases of a distinctive lesion of the Peutz-Jeghers syndrome. Am J Surg Pathol. 2007;31(6):827–35. https://doi.org/10.1097/PAS.0b013e3180309e33.
26. Riegert-Johnson D, Gleeson FC, Westra W, Hefferon T, Wong Kee Song LM, Spurck L, et al. Peutz-Jeghers syndrome. In: Riegert-Johnson DL, Boardman LA, Hefferon T, Roberts M, editors. Cancer syndromes. Bethesda, MD: National Center for Biotechnology Information; 2009.

27. Resta N, Pierannunzio D, Lenato GM, Stella A, Capocaccia R, Bagnulo R, et al. Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study. Dig Liver Dis. 2013;45(7):606–11. https://doi.org/10.1016/j.dld.2012.12.018.
28. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6):1258–64.; ; author reply 65. https://doi.org/10.1038/ajg.2009.725.
29. Grant RC, Selander I, Connor AA, Selvarajah S, Borgida A, Briollais L, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148(3):556–64. https://doi.org/10.1053/j.gastro.2014.11.042.
30. Skaro M, Nanda N, Gauthier C, Felsenstein M, Jiang Z, Qiu M, et al. Prevalence of germline mutations associated with cancer risk in patients with intraductal papillary mucinous neoplasms. Gastroenterology. 2019;156(6):1905–13. https://doi.org/10.1053/j.gastro.2019.01.254.
31. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53. https://doi.org/10.1053/gast.2000.20228.
32. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15. https://doi.org/10.1158/1078-0432.CCR-06-0083.
33. Korsse SE, Harinck F, van Lier MG, Biermann K, Offerhaus GJ, Krak N, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. J Med Genet. 2013;50(1):59–64. https://doi.org/10.1136/jmedgenet-2012-101277.
34. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69(1):7–17. https://doi.org/10.1136/gutjnl-2019-319352.
35. Lynch HT, Krush AJ. Heredity and malignant melanoma: implications for early cancer detection. Can Med Assoc J. 1968;99(1):17–21.
36. Hussussian CJ, Struewing JP, Goldstein AM, Higgins PA, Ally DS, Sheahan MD, et al. Germline p16 mutations in familial melanoma. Nat Genet. 1994;8(1):15–21. https://doi.org/10.1038/ng0994-15.
37. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet. 2007;44(2):99–106. https://doi.org/10.1136/jmg.2006.043802.
38. Villacanas O, Perez JJ, Rubio-Martinez J. Structural analysis of the inhibition of Cdk4 and Cdk6 by p16(INK4a) through molecular dynamics simulations. J Biomol Struct Dyn. 2002;20(3):347–58. https://doi.org/10.1080/07391102.2002.10506853.
39. Soura E, Eliades PJ, Shannon K, Stratigos AJ, Tsao H. Hereditary melanoma: update on syndromes and management: genetics of familial atypical multiple mole melanoma syndrome. J Am Acad Dermatol. 2016;74(3):395–407.; ; quiz 8–10. https://doi.org/10.1016/j.jaad.2015.08.038.
40. Bartsch DK, Sina-Frey M, Lang S, Wild A, Gerdes B, Barth P, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg. 2002;236(6):730–7. https://doi.org/10.1097/00000658-200212000-00005.
41. Lynch HT, Brand RE, Hogg D, Deters CA, Fusaro RM, Lynch JF, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. Cancer. 2002;94(1):84–96. https://doi.org/10.1002/cncr.10159.
42. Ghiorzo P, Fornarini G, Sciallero S, Battistuzzi L, Belli F, Bernard L, et al. CDKN2A is the main susceptibility gene in Italian pancreatic cancer families. J Med Genet. 2012;49(3):164–70. https://doi.org/10.1136/jmedgenet-2011-100281.

43. McWilliams RR, Wieben ED, Rabe KG, Pedersen KS, Wu Y, Sicotte H, et al. Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling. Eur J Hum Genet. 2011;19(4):472–8. https://doi.org/10.1038/ejhg.2010.198.
44. Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B, et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst. 2002;94(12):894–903. https://doi.org/10.1093/jnci/94.12.894.
45. Cust AE, Harland M, Makalic E, Schmidt D, Dowty JG, Aitken JF, et al. Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK. J Med Genet. 2011;48(4):266–72. https://doi.org/10.1136/jmg.2010.086538.
46. Begg CB, Orlow I, Hummer AJ, Armstrong BK, Kricker A, Marrett LD, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. J Natl Cancer Inst. 2005;97(20):1507–15. https://doi.org/10.1093/jnci/dji312.
47. Berwick M, Orlow I, Hummer AJ, Armstrong BK, Kricker A, Marrett LD, et al. The prevalence of CDKN2A germ-line mutations and relative risk for cutaneous malignant melanoma: an international population-based study. Cancer Epidemiol Biomarkers Prev. 2006;15(8):1520–5. https://doi.org/10.1158/1055-9965.EPI-06-0270.
48. Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer. 2000;87(6):809–11.
49. Densham RM, Morris JR. The BRCA1 Ubiquitin ligase function sets a new trend for remodelling in DNA repair. Nucleus. 2017;8(2):116–25. https://doi.org/10.1080/19491034.2016.1267092.
50. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat Rev Cancer. 2011;12(1):68–78. https://doi.org/10.1038/nrc3181.
51. Balmana J, Diez O, Rubio IT, Cardoso F, Group EGW. BRCA in breast cancer: ESMO clinical practice guidelines. Ann Oncol. 2011;22(Suppl 6):vi31–4. https://doi.org/10.1093/annonc/mdr373.
52. Tung NM, Garber JE. BRCA1/2 testing: therapeutic implications for breast cancer management. Br J Cancer. 2018;119(2):141–52. https://doi.org/10.1038/s41416-018-0127-5.
53. Gupta M, Iyer R, Fountzilas C. Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer: a new treatment paradigms and future implications. Cancers (Basel). 2019;11(12):1980. https://doi.org/10.3390/cancers11121980.
54. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329–33. https://doi.org/10.1200/JCO.2006.09.1066.
55. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310–6. https://doi.org/10.1093/jnci/91.15.1310.
56. Oh M, McBride A, Yun S, Bhattacharjee S, Slack M, Martin JR, et al. BRCA1 and BRCA2 gene mutations and colorectal cancer risk: systematic review and meta-analysis. J Natl Cancer Inst. 2018;110(11):1178–89. https://doi.org/10.1093/jnci/djy148.
57. Streff H, Profato J, Ye Y, Nebgen D, Peterson SK, Singletary C, et al. Cancer incidence in first- and second-degree relatives of BRCA1 and BRCA2 mutation carriers. Oncologist. 2016;21(7):869–74. https://doi.org/10.1634/theoncologist.2015-0354.
58. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358–65. https://doi.org/10.1093/jnci/94.18.1358.
59. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42(9):711–9. https://doi.org/10.1136/jmg.2004.028829.
60. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996;56(23):5360–4.
61. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33(28):3124–9. https://doi.org/10.1200/JCO.2014.59.7401.

62. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501. https://doi.org/10.1038/nature14169.
63. Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007;16(2):342–6. https://doi.org/10.1158/1055-9965.EPI-06-0783.
64. Slater EP, Langer P, Fendrich V, Habbe N, Chaloupka B, Matthai E, et al. Prevalence of BRCA2 and CDKN2a mutations in German familial pancreatic cancer families. Fam Cancer. 2010;9(3):335–43. https://doi.org/10.1007/s10689-010-9329-6.
65. Park JY, Singh TR, Nassar N, Zhang F, Freund M, Hanenberg H, et al. Breast cancer-associated missense mutants of the PALB2 WD40 domain, which directly binds RAD51C, RAD51 and BRCA2, disrupt DNA repair. Oncogene. 2014;33(40):4803–12. https://doi.org/10.1038/onc.2013.421.
66. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkas K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497–506. https://doi.org/10.1056/NEJMoa1400382.
67. Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, et al. Cancer risks associated with germline PALB2 pathogenic variants: an international study of 524 families. J Clin Oncol. 2019;38(7):674–85. https://doi.org/10.1200/JCO.19.01907.
68. Fewings E, Larionov A, Redman J, Goldgraben MA, Scarth J, Richardson S, et al. Germline pathogenic variants in PALB2 and other cancer-predisposing genes in families with hereditary diffuse gastric cancer without CDH1 mutation: a whole-exome sequencing study. Lancet Gastroenterol Hepatol. 2018;3(7):489–98. https://doi.org/10.1016/S2468-1253(18)30079-7.
69. Borecka M, Zemankova P, Vocka M, Soucek P, Soukupova J, Kleiblova P, et al. Mutation analysis of the PALB2 gene in unselected pancreatic cancer patients in the Czech Republic. Cancer Genet. 2016;209(5):199–204. https://doi.org/10.1016/j.cancergen.2016.03.003.
70. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009;324(5924):217. https://doi.org/10.1126/science.1171202.
71. Slater EP, Langer P, Niemczyk E, Strauch K, Butler J, Habbe N, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010;78(5):490–4. https://doi.org/10.1111/j.1399-0004.2010.01425.x.
72. Tischkowitz MD, Sabbaghian N, Hamel N, Borgida A, Rosner C, Taherian N, et al. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. Gastroenterology. 2009;137(3):1183–6. https://doi.org/10.1053/j.gastro.2009.06.055.
73. Boohaker RJ, Xu B. The versatile functions of ATM kinase. Biomed J. 2014;37(1):3–9. https://doi.org/10.4103/2319-4170.125655.
74. Gatti R, Perlman S. Ataxia-telangiectasia. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews((R)). Seattle, WA: University of Washington; 1993.
75. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243–57. https://doi.org/10.1056/NEJMsr1501341.
76. Jerzak KJ, Mancuso T, Eisen A. Ataxia-telangiectasia gene (ATM) mutation heterozygosity in breast cancer: a narrative review. Curr Oncol. 2018;25(2):e176–e80. https://doi.org/10.3747/co.25.3707.
77. van Os NJ, Roeleveld N, Weemaes CM, Jongmans MC, Janssens GO, Taylor AM, et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet. 2016;90(2):105–17. https://doi.org/10.1111/cge.12710.
78. Roberts NJ, Jiao Y, Yu J, Kopelovich L, Petersen GM, Bondy ML, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2(1):41–6. https://doi.org/10.1158/2159-8290.CD-11-0194.

79. Dominguez-Valentin M, Sampson JR, Seppala TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15–25. https://doi.org/10.1038/s41436-019-0596-9.
80. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Curr Treat Options Oncol. 2015;16(7):30. https://doi.org/10.1007/s11864-015-0348-2.
81. Evaluation of Genomic Applications in Practice and Prevention Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11(1):35–41. https://doi.org/10.1097/GIM.0b013e31818fa2ff.
82. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20. https://doi.org/10.1056/NEJMoa1500596.
83. Moller P, Seppala TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018;67(7):1306–16. https://doi.org/10.1136/gutjnl-2017-314057.
84. Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15–25. https://doi.org/10.1038/s41436-019-0596-9.
85. Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. JAMA. 2019;322(24):2422–34. https://doi.org/10.1001/jama.2019.19411.
86. Jalaly NY, Moran RA, Fargahi F, Khashab MA, Kamal A, Lennon AM, et al. An evaluation of factors associated with pathogenic PRSS1, SPINK1, CTFR, and/or CTRC genetic variants in patients with idiopathic pancreatitis. Am J Gastroenterol. 2017;112(8):1320–9. https://doi.org/10.1038/ajg.2017.106.
87. Tamura K, Yu J, Hata T, Suenaga M, Shindo K, Abe T, et al. Mutations in the pancreatic secretory enzymes CPA1 and CPB1 are associated with pancreatic cancer. Proc Natl Acad Sci U S A. 2018;115(18):4767–72. https://doi.org/10.1073/pnas.1720588115.
88. Kirkegard J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol. 2017;112(9):1366–72. https://doi.org/10.1038/ajg.2017.218.
89. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016;122(23):3673–81. https://doi.org/10.1002/cncr.30248.
90. Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018;30(1):23–9. https://doi.org/10.1097/CCO.0000000000000423.
91. Ruijs MW, Verhoef S, Rookus MA, Pruntel R, van der Hout AH, Hogervorst FB, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. J Med Genet. 2010;47(6):421–8. https://doi.org/10.1136/jmg.2009.073429.
92. Frebourg T, Lagercrantz SB,Oliveira C, Magenheim R,Evans GD, European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020. https://doi.org/10.1038/s41431-020-0638-4.
93. Aihara H, Kumar N, Thompson CC. Diagnosis, surveillance, and treatment strategies for familial adenomatous polyposis: rationale and update. Eur J Gastroenterol Hepatol. 2014;26(3):255–62. https://doi.org/10.1097/MEG.0000000000000010.

94. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker SV, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut. 1993;34(10):1394–6. https://doi.org/10.1136/gut.34.10.1394.
95. Groen EJ, Roos A, Muntinghe FL, Enting RH, de Vries J, Kleibeuker JH, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol. 2008;15(9):2439–50. https://doi.org/10.1245/s10434-008-9981-3.
96. Thibodeau ML, Zhao EY, Reisle C, Ch'ng C, Wong HL, Shen Y, et al. Base excision repair deficiency signatures implicate germline and somatic MUTYH aberrations in pancreatic ductal adenocarcinoma and breast cancer oncogenesis. Cold Spring Harb Mol Case Stud. 2019;5(2):a003681. https://doi.org/10.1101/mcs.a003681.
97. Nissim S, Leshchiner I, Mancias JD, Greenblatt MB, Maertens O, Cassa CA, et al. Mutations in RABL3 alter KRAS prenylation and are associated with hereditary pancreatic cancer. Nat Genet. 2019;51(9):1308–14. https://doi.org/10.1038/s41588-019-0475-y.
98. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30.

Chapter 4
Familial Pancreatic Cancer

Nicholas J. Roberts and Laura D. Wood

Take Home Messages

- PDACs occurring in families with a pair of affected first-degree relatives are termed "familial pancreatic cancer".
- Pathogenic germline variants in pancreatic cancer susceptibility genes are frequently identified in patients with familial pancreatic cancer, sporadic PDAC, and IPMNs.
- The most prevalent pathogenic germline variants in patients with PDAC and IPMN are in *ATM* and *BRCA2*.
- The genetic basis for the majority of familial pancreatic cancer remains to be discovered.

Future Perspectives

- Unbiased, gene sequencing studies in large cohorts of patients with PDAC are needed to identify additional pancreatic cancer susceptibility genes.
- The contribution of variants of unknown significance and non-coding (e.g. promoter and intronic) variants in pancreatic cancer susceptibility genes to risk of pancreatic cancer should be defined with epidemiological, computational, and functional studies.
- Age-specific penetrance estimates for developing PDAC, with and without a family history of the disease, should be established for all pancreatic

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cancer susceptibility genes to aid risk assessment and inform early detection efforts in carriers of pathogenic germline variants.
- The role of pathogenic germline variants in pancreatic cancer susceptibility genes in the progression of IPMN and the clinical utility of germline status to stratify patients with IPMN for clinical intervention should be determined.
- Optimal mutation-based screening protocols for carriers of pathogenic germline variants need to be established.

4.1 Introduction

Pancreatic tumorigenesis is influenced by inherited (germline) variation, environmental risk factors, and stochastic effects. Knowledge of a patient's underlying susceptibility to pancreatic cancer due to highly penetrant germline variants in pancreatic cancer susceptibility genes has quickly become an essential component of patient care for individuals with pancreatic ductal adenocarcinoma (PDAC) and for their relatives. Specifically, patients with PDAC and a pathogenic germline variant in *BRCA1*, *BRCA2*, or *PALB2* have tumors that are more sensitive to certain chemotherapeutic agents or poly(ADP)-ribose polymerase (PARP) inhibitors due to deficiency in homology-directed DNA repair [1, 2]. Moreover, patients with PDAC and a pathogenic germline variant in *MLH1, MSH2, MSH6, or PMS2* have tumors with a high somatic mutation burden that are uniquely sensitive to immunotherapy [3].

For relatives of patients with PDAC, clinical surveillance to detect PDAC and other cancers early, when clinical intervention is more often curative, may be warranted based on their germline status. However, while many established and candidate pancreatic cancer susceptibility genes have been discovered, our understanding of the genetic etiology of inherited risk of PDAC remains incomplete.

In this chapter we review inherited risk of PDAC in patients with and without a family history of the disease and discuss the implications for disease screening in carriers of pathogenic germline variants in pancreatic cancer susceptibility genes.

4.2 Familial Pancreatic Cancer

Familial clustering of PDACs has been described in multiple kindreds, indicating an inherited component to risk of PDAC [4–6]. Up to 10% of PDACs occur in families with a pair of affected first-degree relatives and are termed "familial pancreatic cancer" [7]. A family history of pancreatic cancer is a strong risk factor for developing the disease, with risk of PDAC increasing with the number of first-degree relatives affected. In a study by the National Familial Pancreatic Tumor Registry (NFPTR) at Johns Hopkins University, standardized incidence ratio was highest for individuals with 3 or more affected first-degree relatives at 32.0 (95% confidence interval: 10.2–74.7) [8]. Consequently, much research has been conducted to identify the underlying genetic etiology of familial pancreatic cancer. These efforts have

led to the identification of several pancreatic cancer susceptibility genes and include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *PRSS1*, *STK11*, and *TP53*. Furthermore, multiple candidate genes have recently been identified and require validation in independent cohorts of pancreatic cancer patients to determine their clinical utility. These candidate genes include *BUB1B*, *CPA1*, *CPB1*, *FANCC*, *FANCG*, *RABL3*, and *SMG1* [9–12]. Despite these advances, pathogenic germline variants in these genes are observed in only approximately 20% of familial pancreatic cancer patients [9]. As up to 50% of familial pancreatic cancer patients are thought to have an inherited predisposition to pancreatic cancer due to a rare, high-risk, autosomal dominant gene, additional pancreatic cancer susceptibility genes are yet to be identified [13].

4.3 Pancreatic Cancer Susceptibility Genes in Patients with Familial Pancreatic Cancer

4.3.1 ATM

Pathogenic germline *ATM* variants are associated with an increased risk of pancreatic cancer as well as breast cancer, stomach cancer, and lethal prostate cancer [14–17]. The association between pathogenic germline *ATM* variants and risk of pancreatic cancer was first conclusively identified using whole genome and whole exome sequencing of patients with familial pancreatic cancer, where 2 of 16 families sequenced harbored rare premature truncating variants that segregated with disease [14]. The association between pathogenic germline variants in *ATM* and risk of pancreatic cancer was subsequently validated in several studies, with 1.0–3.7% of patients with familial pancreatic cancer carrying a pathogenic germline *ATM* variant (Table 4.1) [9, 14, 18, 19]. Interestingly, while pancreatic tumors from patients with a pathogenic germline variant in *ATM* are histologically diverse, a preponderance of colloid carcinomas has been observed and may identify patients for germline testing or help interpret equivocal genetic test results as occurs with identification of variants of unknown significance [20]. The penetrance of pancreatic cancer in

Table 4.1 Studies assessing prevalence of pathogenic germline *ATM* variants in patients with familial pancreatic cancer

Reference	Patient population[a]	Number of patients	Number of patients with a pathogenic *ATM* variant
[37]	FH+/FH−	290	3
[9]	FH+	638	21
[18]	FH+	54	2
[19]	FH+/FH−	3030	69

[a]*FH+* family history of pancreatic cancer sufficient for classification as familial pancreatic cancer; *FH−* no family history of pancreatic cancer or family history of pancreatic cancer insufficient for classification as familial pancreatic cancer

individuals with a pathogenic germline variant in *ATM*, including age-specific estimates important for risk assessment and clinical management of patients, have not been defined. However, a recent study using a germline targeted gene sequencing panel on over 3000 patients with pancreatic cancer unselected for family history defined an odds ratio of 5.7 (95% confidence interval 4.4–7.3) [19]. It is currently unknown whether risk of pancreatic cancer differs in patients with a pathogenic germline *ATM* variant based on cancer family history.

4.3.2 BRCA1, BRCA2, PALB2

BRCA1, *BRCA2*, and *PALB2* are critical components of DNA double strand break repair pathways, and pathogenic germline variants are associated with pancreatic cancer as well as cancers of the breast and ovary, among others. Pathogenic germline variants in *BRCA2* are the most prevalent inherited cause of familial pancreatic cancer, being found in 3.7–16.7% of patients with familial pancreatic cancer [21–23]. Pathogenic germline variants in *BRCA1* and *PALB2* are much less frequent in patients with familial pancreatic cancer, with reported prevalence of 1.1–9.5% for pathogenic germline *BRCA1* variants and 0.5–3.7% for pathogenic germline *PALB2* variants [21–25]. Penetrance estimates for pancreatic cancer in patients with a pathogenic germline variant in *BRCA1*, *BRCA2*, or *PALB2* are poorly defined. Recent odds ratio estimates for *BRCA2* (6.2; 95% confidence interval 4.6–8.2), *BRCA1* (2.6; 95% confidence interval 1.5–4.1), and *PALB2* (2.3; 95% confidence interval 1.2–4.0) in a large cohort of PDAC patients unselected for family history, however, are in keeping with earlier odds ratio estimates in patients with familial pancreatic cancer [19, 26].

4.3.3 CDKN2A

Patients with pathogenic germline variants in *CDKN2A* (also known as p16) have familial atypical multiple mole melanoma (FAMMM) syndrome. As suggested by the name, the most common neoplasms in patients with this syndrome are melanocytic in origin, but FAMMM patients also have an increased risk of pancreatic cancer. A characteristic 19 base pair deletion in exon 2 of *CDKN2A* occurs in Dutch families and is referred to as p16-Leiden—patients with this deletion have a 17% lifetime risk of development of pancreatic cancer [27]. However, pancreatic cancer is not a universal feature of FAMMM, and except for p16-Leiden, the relationship between specific *CDKN2A* sequence alterations and pancreatic cancer risk is incompletely understood, as most pathogenic germline variants occur in a single family [28]. The risk of pancreatic cancer in carriers of pathogenic germline *CDKN2A* variants varies with geography, with high risk in Northern Europe and low risk in Australia, likely reflecting differential risk between distinct founder mutations in

different populations [29]. Still the high risk in p16-Leiden families highlights the potential impact of pathogenic germline *CDKN2A* variants in pancreatic cancer risk.

4.3.4 Hereditary Pancreatitis Genes

Patients with hereditary pancreatitis are also at increased risk for the development of pancreatic cancer. Pathogenic germline variants in *PRSS1*, which encodes cationic trypsinogen, cause severe chronic pancreatitis with an early age of onset [30]. Moreover, patients with pathogenic germline *PRSS1* variants have a markedly increased lifetime risk of pancreatic cancer, approximately 40% by age 70, likely due to repeated rounds of inflammation, injury, and repair in the pancreas [31]. Patients with pathogenic germline variants in *SPINK1* and *CFTR* also have a hereditary pancreatitis phenotype, but the link to pancreatic cancer for these genes is less well developed. Intriguingly, while patients with bi-allelic pathogenic *CFTR* variants have cystic fibrosis with exocrine pancreatic insufficiency, heterozygous pathogenic *CFTR* variants have been identified in young patients with idiopathic chronic pancreatitis without other features of cystic fibrosis [32]. In addition, pathogenic germline variants in the pancreatic secretory enzymes *CPA1* and *CPB1* have recently been reported at higher prevalence in pancreatic cancer patients compared to controls, suggesting that such mutations increase the risk of pancreatic cancer [10]. Although variants of *CPA1* have been associated with the development of pancreatitis, pancreatic cancer can also develop without features of pancreatitis in patients with such pathogenic variants [10].

4.3.5 Other Inherited Syndromes

Increased risk of pancreatic cancer is a component of multiple well-described inherited syndromes. One of the clinically most important of these is Peutz Jeghers syndrome, which is caused by pathogenic germline variants in the serine-threonine kinase *STK11/LKB1* and results in a strikingly increased pancreatic cancer risk (~30% lifetime risk of pancreatic cancer) [33].

Another syndrome with critical clinical implications is Lynch syndrome (also known as Hereditary Nonpolyposis Colon Cancer or HNPCC), an inherited cancer predisposition syndrome caused by pathogenic germline variants in genes encoding DNA mismatch repair machinery (*MLH1, MSH2, MSH6,* and *PMS2*). Although colorectal and uterine cancers are the most common tumor types in Lynch syndrome patients, these patients have an increased risk of many cancer types, including >8-fold increased risk of pancreatic cancer [34]. Pancreatic cancers in Lynch syndrome patients can have a characteristic medullary histology, and the increased tumor mutation burden in tumors with microsatellite instability raises the possibility of response to immune checkpoint inhibitor therapy [3, 35]. Pancreatic cancers in

the setting of known inherited genetic syndromes are covered in detail in a separate chapter.

4.4 Pancreatic Cancer Susceptibility Genes in Patients with Sporadic PDAC

Inherited risk of pancreatic cancer is not limited to patients with a family history of the disease. Initial evidence for a role of pathogenic germline variants in pancreatic cancer susceptibility genes in patients with apparently sporadic PDAC, that is those without a family history that would result in classification as familial pancreatic cancer, came from targeted sequencing of *BRCA2* in a cohort of 41 patients without a family history of PDAC [36]. In this study, three patients had pathogenic germline *BRCA2* variants with corresponding loss-of-heterozygosity of the *BRCA2* genomic locus involving the wildtype allele. Subsequently, several studies using targeted next generation sequencing gene panels have defined the prevalence of pathogenic germline variants in pancreatic cancer susceptibility genes in patients without a family history of the disease (Table 4.2) [19, 36–46]. While these studies used next generation sequencing targeted panels with variable gene content, pathogenic germline variants in pancreatic cancer susceptibility genes were identified in 3.6–19.4% of patients with sporadic pancreatic cancer, with pathogenic variants in *ATM* and *BRCA2* the most frequently identified. This finding has significant implications for the treatment of the patients and the clinical surveillance of relatives. As such, National Comprehensive Cancer Network Clinical Guidelines were updated to recommend consideration of germline testing for all patients diagnosed with PDAC irrespective of family history [47].

4.5 Pancreatic Cancer Susceptibility Genes in Patients with Pancreatic Cancer Precursor Lesions

Pancreatic cancers develop from either microscopic precursor lesions called pancreatic intraepithelial neoplasms (PanINs) or macroscopic precursor lesions called intraductal papillary mucinous neoplasms (IPMNs). As IPMNs are macroscopic, they can be monitored and surgically resected if clinical features are suggestive of progression to PDAC [48, 49]. While several recent studies have focused on the prevalence of germline alterations in patients with PDAC, the role of pancreatic cancer susceptibility genes in patients with IPMN is less well understood. Case reports of patients with IPMN and pathogenic germline variants in pancreatic cancer susceptibility genes have suggested an association [50–52]. In a recent study of 315 patients with surgically resected IPMN, 2.7% of patients had a pathogenic germline variant in a pancreatic cancer susceptibility gene, most frequently *ATM* (1.6%) [53]. While these observations are similar to prevalence estimates for

Table 4.2 Studies assessing prevalence of pathogenic germline variants in pancreatic cancer susceptibility genes in patients with sporadic PDAC

Study	Patient population[a]	Number of patients	Pancreatic cancer susceptibility genes assessed	Number of patients with a pathogenic variant
[36]	Unselected	41	*BRCA2*	3
[37]	FH+/FH−	290	*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, PRSS1, STK11, and TP53*	11
[38]	Unselected	306	*BRCA1; BRCA2*	14
[39]	Unselected	96	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*	9
[40]	Unselected	159	*BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, and PMS2*	24
[41]	Unselected	854	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*	31
[19]	FH+/FH−	3030	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, and TP53*	189
[42]	Unselected	356	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*	69
[43]	Unselected	176	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*	26
[44]	Unselected	350	*ATM, BRCA1, BRCA2, and PALB2*	16
[45]	Unselected	3594	*ATM; BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*	258
[46]	Unselected	289	*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, PRSS1, STK11, and TP53*	18

[a]*FH+* family history of pancreatic cancer sufficient for classification as familial pancreatic cancer; *FH−* no family history of pancreatic cancer or family history of pancreatic cancer insufficient for classification as familial pancreatic cancer

patients with sporadic PDAC or PDAC unselected for family history, the clinical utility of germline status in patients with IPMN is not yet known.

4.6 Screening for Patients with Pathogenic Germline Variants

Knowledge of germline status of established pancreatic cancer susceptibility genes should inform screening approaches for high-risk patients. Screening in a large cohort of high-risk individuals (including those with pathogenic germline variants and those with a family history of PDAC) demonstrated lower stage and improved survival in PDACs detected during surveillance compared to those

detected outside of surveillance [54]. In this study, the cumulative incidence of high-grade precursor lesion or PDAC was 6.5% over a median follow-up of 5.6 years [54]. Moreover, the risk of pancreatic cancer is more than two times higher in individuals with an identifiable pathogenic germline variant in a pancreatic cancer susceptibility gene compared to individuals with a family history but no identifiable pathogenic variant, further highlighting the need for screening in this patient population [55].

Individuals with a pathogenic germline variant have an earlier age at diagnosis than other high-risk individuals, and thus screening should start earlier in such patients [55]. Recent consensus guidelines suggest that individuals with pathogenic germline variants in *ATM, BRCA2,* and *PALB2* should undergo surveillance if they have a blood relative with pancreatic cancer, while those with pathogenic germline variants in *CDKN2A* or *STK11* (Peutz Jeghers syndrome) should undergo screening regardless of family history because of their high lifetime risk [56]. While there was consensus that individuals with pathogenic germline *BRCA1* variants should be screened, consensus could not be reached as to the impact of family history on surveillance recommendations [56]. Furthermore, whether patients with a pathogenic germline variant in a pancreatic cancer susceptibility gene without a family history of pancreatic cancer should undergo screening is yet to be determined.

For most carriers of a pathogenic germline variant, current consensus recommends that annual surveillance begin at age 50, though some experts recommend an earlier initiation of surveillance. In addition, for some specific genes with increased risk, surveillance should begin earlier—at age 40 for carriers of a pathogenic *CDKN2A* variant and at age 30–40 for individuals with Peutz Jeghers syndrome [56]. In addition to these pancreatic cancer susceptibility genes, surveillance is also recommended for patients with hereditary pancreatitis, including pathogenic germline variants in *PRSS1* and *CPA1*, beginning at age 40 or 20 years after the onset of pancreatitis symptoms [56]. Surveillance is also recommended for patients with a family history of pancreatic cancer in the absence of identifiable pathogenic germline variants [56].

Though there is still considerable controversy regarding the optimal surveillance approach, most protocols use a combination of magnetic resonance imaging (MRI)/magnetic retrograde cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) [56]. Computed tomography is considered a suboptimal approach due to decreased sensitivity in detecting small pancreatic cysts as well as exposure to repeated ionizing radiation, though future advances in deep learning and radiomics may improve the utility of this imaging modality [56]. Other potentially promising complementary screening tests include serum CA19-9, markers of prediabetes (including fasting serum glucose and hemoglobin A1C), and circulating tumor DNA, though their utility has not yet been directly evaluated in high-risk individuals with pathogenic germline variants in pancreatic cancer susceptibility genes [56].

4.7 Conclusion

Pathogenic germline variants in cancer susceptibility genes are frequently identified in patients with familial pancreatic cancer and less frequently in patients with apparently sporadic PDAC. Several key pancreatic cancer susceptibility genes have been identified and characterized in detail, but the genetic basis for the majority of familial pancreatic cancer is not yet known. Known susceptibility genes have important implications for the treatment of arising PDACs, as well as screening for affected family members. Future work will identify new pancreatic cancer susceptibility genes, characterize the impact of noncoding variants and those of unknown significance, and further optimize screening protocols for patients at high risk for pancreatic cancer.

References

1. Villarroel MC, Rajeshkumar NV, Garrido-Laguna I, et al. Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer. Mol Cancer Ther. 2011;10:3–8.
2. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317–27.
3. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20.
4. MacDermott RP, Kramer P. Adenocarcinoma of the pancreas in four siblings. Gastroenterology. 1973;65:137–9.
5. Katkhouda N, Mouiel J. Pancreatic cancer in mother and daughter. Lancet. 1986;2:747.
6. Reimer RR, Fraumeni JF Jr, Ozols RF, et al. Pancreatic cancer in father and son. Lancet. 1977;1:911.
7. Klein AP. Identifying people at a high risk of developing pancreatic cancer. Nat Rev Cancer. 2013;13:66–74.
8. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004;64:2634–8.
9. Roberts NJ, Norris AL, Petersen GM, et al. Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov. 2016;6:166–75.
10. Tamura K, Yu J, Hata T, et al. Mutations in the pancreatic secretory enzymes CPA1 and CPB1 are associated with pancreatic cancer. Proc Natl Acad Sci U S A. 2018;115:4767–72.
11. Nissim S, Leshchiner I, Mancias JD, et al. Mutations in RABL3 alter KRAS prenylation and are associated with hereditary pancreatic cancer. Nat Genet. 2019;51:1308–14.
12. Wong C, Chen F, Alirezaie N, et al. A region-based gene association study combined with a leave-one-out sensitivity analysis identifies SMG1 as a pancreatic cancer susceptibility gene. PLoS Genet. 2019;15:e1008344.
13. Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog. 2012;51:14–24.
14. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012;2:41–6.
15. Swift M, Morrell D, Massey RB, et al. Incidence of cancer in 161 families affected by ataxia-telangiectasia. N Engl J Med. 1991;325:1831–6.
16. Helgason H, Rafnar T, Olafsdottir HS, et al. Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet. 2015;47:906–10.

17. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol. 2017;71:740–7.
18. Takai E, Yachida S, Shimizu K, et al. Germline mutations in Japanese familial pancreatic cancer patients. Oncotarget. 2016;7:74227–35.
19. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA. 2018;319:2401–9.
20. Hutchings D, Jiang Z, Skaro M, et al. Histomorphology of pancreatic cancer in patients with inherited ATM serine/threonine kinase pathogenic variants. Mod Pathol. 2019;32:1806–13.
21. Zhen DB, Rabe KG, Gallinger S, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. Genet Med. 2015;17:569–77.
22. Chaffee KG, Oberg AL, McWilliams RR, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. Genet Med. 2018;20:119–27.
23. Catts ZA, Baig MK, Milewski B, et al. Statewide retrospective review of familial pancreatic cancer in Delaware, and frequency of genetic mutations in pancreatic cancer kindreds. Ann Surg Oncol. 2016;23:1729–35.
24. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009;324:217.
25. Slater EP, Langer P, Niemczyk E, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010;78:490–4.
26. Chen F, Roberts NJ, Klein AP. Inherited pancreatic cancer. Chin Clin Oncol. 2017;6:58.
27. Vasen HF, Gruis NA, Frants RR, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer. 2000;87:809–11.
28. Goldstein AM. Familial melanoma, pancreatic cancer and germline CDKN2A mutations. Hum Mutat. 2004;23:630.
29. Goldstein AM, Chan M, Harland M, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet. 2007;44:99–106.
30. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet. 1996;14:141–5.
31. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89:442–6.
32. Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med. 1998;339:653–8.
33. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119:1447–53.
34. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302:1790–5.
35. Wilentz RE, Goggins M, Redston M, et al. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: a newly described and characterized entity. Am J Pathol. 2000;156:1641–51.
36. Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996;56:5360–4.
37. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148:556–64.
38. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33:3124–9.
39. Hu C, Hart SN, Bamlet WR, et al. Prevalence of pathogenic mutations in cancer predisposition genes among pancreatic cancer patients. Cancer Epidemiol Biomark Prev. 2016;25:207–11.
40. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer. 2015;121:4382–8.

41. Shindo K, Yu J, Suenaga M, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol. 2017;35:3382–90.
42. Lowery MA, Wong W, Jordan EJ, et al. Prospective evaluation of germline alterations in patients with exocrine pancreatic neoplasms. J Natl Cancer Inst. 2018;110:1067–74.
43. Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA. 2017;318:825–35.
44. Smith AL, Wong C, Cuggia A, et al. Reflex testing for germline BRCA1, BRCA2, PALB2, and ATM mutations in pancreatic cancer: mutation prevalence and clinical outcomes from two Canadian research registries. JCO Precis Oncol. 2018;2:1–16.
45. Singhi AD, George B, Greenbowe JR, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might be targeted with existing drugs or used as biomarkers. Gastroenterology. 2019;156:2242–53. e4
46. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21:213–23.
47. Tempero MA. NCCN guidelines updates: pancreatic cancer. J Natl Compr Cancer Netw. 2019;17:603–5.
48. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738–53.
49. Vege SS, Ziring B, Jain R, et al. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:819–22; quiz e12–3.
50. Martinez de Juan F, Reolid Escribano M, Martinez Lapiedra C, et al. Pancreatic adenosquamous carcinoma and intraductal papillary mucinous neoplasm in a CDKN2A germline mutation carrier. World J Gastrointest Oncol. 2017;9:390–6.
51. Sato N, Rosty C, Jansen M, et al. STK11/LKB1 Peutz-Jeghers gene inactivation in intraductal papillary-mucinous neoplasms of the pancreas. Am J Pathol. 2001;159:2017–22.
52. Lubezky N, Ben-Haim M, Lahat G, et al. Intraductal papillary mucinous neoplasm of the pancreas: associated cancers, family history, genetic predisposition? Surgery. 2012;151:70–5.
53. Skaro M, Nanda N, Gauthier C, et al. Prevalence of germline mutations associated with cancer risk in patients with intraductal papillary mucinous neoplasms. Gastroenterology. 2019;156:1905–13.
54. Canto MI, Almario JA, Schulick RD, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology. 2018;155:740–51.e2.
55. Abe T, Blackford AL, Tamura K, et al. Deleterious germline mutations are a risk factor for neoplastic progression among high-risk individuals undergoing pancreatic surveillance. J Clin Oncol. 2019;37:1070–80.
56. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69:7–17.

Part II
Education, Training and Quality of Care

Chapter 5
Education and Training in Pancreatic Surgery

Rowan W. Parks and Rachel V. Guest

Take Home Messages
- Further subspecialty training in pancreatic surgery following accreditation is sought by the majority of trainees before independent practice.
- Several routes of entry are available to advanced pancreatic fellowships.
- International and Regional Specialty Associations seek to improve education and training in pancreatic surgery across the globe.
- eLearning and social media are playing an increasing role in the education of pancreatic surgeons.

Pearls and Pitfalls
- Standards for training in pancreatic surgery have been set by IHPBA.
- Training opportunities and standards in pancreatic surgical training vary widely outside of North America, Europe and Australasia.

Future Perspectives
- An agreed structured curriculum for training in minimally invasive pancreatic surgery would formalise attainment of learning and proficiency curves.
- Summative assessment is currently a requirement of a small number of fellowships worldwide but may become more widespread as an objective measure of training quality.
- 'Altmetrics' generated through social media are likely to become an alternative output for measuring the scope and reach of academic output.

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Bullet Points

Structure of Training Pathways

- Accreditation in pancreatic surgery necessitates additional training beyond residency in General Surgery
- A number of routes to pancreatic fellowship exist including surgical oncology, transplantation and bespoke HPB programmes
- Accredited schemes should follow a pre-determined curriculum and offer minimum caseload volume
- Currently an HPB-specific postgraduate qualification is not considered necessary for independent practice

Standards of Training

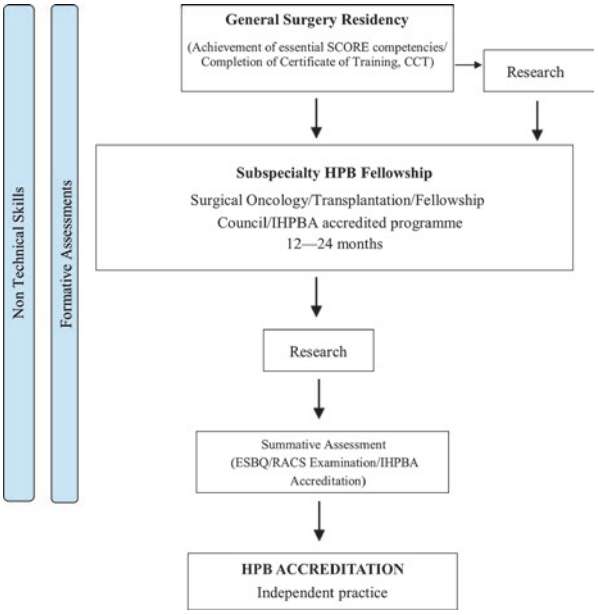
- Pancreatic fellowships typically require 12 – 24 months of additional training beyond residency
- Syllabus and curricula are suggested by IHPBA and UEMS to guide both fellows and training units
- The use of formative assessments is highly recommended in evaluating trainee performance
- Summative assessment is not currently mandatory for pancreatic fellowship evaluation

Clinical Experience & Skills Acquisition

- Competency is suggested to be achievable after 20 pancreatoduodenectomy procedures; proficiency after 60 but it is recognised that such numbers are highly variable and subject to the trainee experience
- Training in Non Technical Surgical Skills (NOTSS) is highly desirable

Research

- A higher degree is not a requirement for entry into pancreatic fellowship programmes
- Research is mandatory in all IHPBA accredited pancreatic fellowship schemes



5.1 Structure of Training Pathways

Exposure to complex pancreatic procedures during General Surgical residency is frequently limited, or at least insufficient for independent practice [1–3]. Trainees' exposure to HPB procedures during General Surgery training has become dominated by cholecystectomy, and experience of complex pancreatic procedures is reducing [3]. Recognition that the technical complexity and morbidity associated with pancreatic surgery necessitates additional years of training beyond accreditation in General Surgery has led to the world-wide development of advanced postgraduate fellowships in HPB surgery [4]. Dozens of such HPB fellowships across 18 countries are currently registered by the International Hepato-Pancreatio-Biliary Association (IHPBA) [5]. The route to HPB accreditation varies not just globally but also at a national level.

5.1.1 North-American Training Programmes

In North America, entry to HPB fellowship programmes occurs via one of three principal avenues. HPB surgical training is undertaken in parallel with training in either transplantation or surgical oncology; approved and regulated by the American Society of Transplant Surgeons (ASTS), the Society of Surgical Oncology (SSO) or the Accreditation Council for Graduate Medical Education (ACGME). More recently, the Fellowship Council has developed non-ACGME HPB fellowship programmes designed to provide bespoke multidisciplinary HPB training that includes experience in minimally invasive surgery (MIS), ablation techniques and ultrasonography. The Fellowship Council is an association of programme directors and specialty societies charged with oversight of fellowship training in the US and has developed accreditation criteria and curricula in collaboration with sponsoring societies such as the Americas Hepato-Pancreato-Biliary Association (AHPBA). Each fellowship programme offers its own case mix of liver, biliary and pancreatic exposure, and various strengths and weaknesses have been claimed for each of the three approaches [6]. For example, fellows training in transplantation develop an understanding of organ failure and parenchymal liver disease whereas fellows in surgical oncology evolve as clinicians managing patients with cancer [6]. The majority of HPB surgeons will establish a complementary parallel practice in transplantation, surgical oncology or general surgery and therefore it is felt that this current structure reflects their future likely practice and as such remains a good model for fellowship training programmes.

In Latin America, subspecialty fellowships similarly exist, including a number of AHPBA accredited programmes in Argentina, Brazil, Mexico and Peru [5], however availability of training opportunities and standards vary widely.

5.1.2 European Training Programmes

In Europe, training in pancreatic surgery is not formally organised under one regulatory body, however the European and African Hepato-Pancreato-Biliary Association (E-AHPBA) supports the educational activities of its members through provision of a suggested HPB curriculum, accreditation of HPB centres that host fellowship programmes and organisation of the European Board of Surgery Qualification (EBSQ) on behalf of the Union Européenes des Médicines Spécialistes (UEMS) [5]. Such certification is not required for independent practice; European Union (EU) law determines that all EU national surgical qualifications are recognised between member EU states, however training experience and standards are acknowledged to vary widely across Europe and therefore surgeons frequently choose to obtain a EBSQ for global recognition of a standardised qualification.

In the United Kingdom (UK), no specific subspecialty qualification is required for an independent clinical practice that includes pancreatic surgery. All trainees undertake training in General Surgery which commonly includes a 1–2-year period in their subspecialty of choice towards the end of training; leading ultimately to a 'Certificate of Completion of Training' (CCT) awarded by the Joint Committee on Surgical Training (JCST), an advisory body to the four surgical Royal Colleges of the UK and Ireland. As in North America, trainees with an interest in HPB surgery frequently at this stage do not feel fully prepared for autonomous HPB practice and therefore seek a further year of subspecialty training in a fellowship position, often undertaken outside the UK.

5.1.3 Australasian Programmes

A similar but more formalised infrastructure exists in Australia and New Zealand, where trainees undertake a 2-year HPB fellowship with competitive entry, following or during general surgical training. Programmes are accredited by the Royal Australasian College of Surgeons (RACS) and adhere to a structured curriculum, include a requirement for research, the successful achievement of an expected minimum caseload and an end-of-programme examination [5].

In Asia, opportunities for training fellowships are organised on a national rather than continental level. The Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA) seeks to 'improve education, training, innovation and patient care in the field of HPB' and has adopted the IHPBA curriculum for training. It disseminates information on fellowships through the IHPBA fellowship registry but does not oversee individual programmes.

5.1.4 *Effect of Training Programmes on Clinical Outcomes*

Retrospective studies indicate that the presence of a subspecialty fellow in HPB units results in at least equivalent or even enhanced patient outcomes [7–9]. Such studies are of course limited by selection bias and confounders including case mix, specialist anaesthetic and critical care infrastructure, and the ability to attract high-quality fellows to units of excellence. As subspecialty fellowship programmes are, by convention, co-ordinated and run by tertiary referral centres, frequently with university affiliation and high-volume caseload, it is arguable that it is impracticable to disentangle any potential effects of the subspecialty HPB fellow on patient outcomes or quality indicators. One barrier to achieving operative autonomy in the operating room that has been identified is the requirement of trainees to adopt dual roles; those of 'learner' and 'worker' [10]. As resident engagement is the single factor most predictive of developing independence, it seems likely that the subspecialty fellowship offers a chance for trainees to identify as pure 'learners', free from some of the duties of General Surgical residency and to focus on pancreatic surgery. The presence of a specialist HPB fellow need not be to the detriment of the training of local General Surgery residents [11, 12]. Indeed, when matched for surgeon and case volume, centres with residency training programmes appear to have superior outcomes following pancreatoduodenectomy compared to centres without such schemes, as measured by length of stay, in-hospital mortality and cost [9].

5.1.5 *Workforce Prediction*

Accurate predictions on workforce requirements for healthcare personnel are difficult to achieve [13]. Studies examining the HPB surgical workforce in the US have demonstrated that the trend of increasing HPB case volume has outpaced projections; a phenomenon attributed to expanding indications for surgery and increasing centralisation of HPB services [14, 15]. In parallel, the number of HPB subspecialty fellowships has risen, however surgeons reaching the end of subspecialty fellowships are more frequently reporting perceptions that HPB faculty positions are increasingly challenging to secure [14]. Although some have raised concerns that the increased numbers of graduating HPB fellows will outstrip demand [15, 16], others suggest that despite the ongoing trends towards centralisation of services, large regions of the US remain underserved in terms of HPB specialists [17]. Elevation and standardisation of HPB accreditation requirements have been suggested as solutions to this problem as an alternative to capping fellowship numbers, with more focus on improving outcomes and enhanced provision of services in underserved communities [14, 17].

5.2 Standards of Training

The International Hepato-Pancreato-Biliary Association (IHPBA), established in 1994, is a non-profit organisation whose declared mission is to optimise the outcomes of patients with HPB disorders by improving education, training, innovation, research and the delivery of patient care [18]. A similar strategy is pursued by the European Society of Surgical Oncology (ESSO), which seeks to develop links with academic institutions across Europe, organises educational opportunities (including courses and postgraduate fellowships) and offers recognisable diplomas with transferable value. The IHPBA Education and Training (E&T) Committee has defined a set of standardised training requirements to ensure high quality training across countries, and facilitates institutions registering their advanced HPB training fellowships for accreditation [5]. Standards for training were drawn up and agreed by consensus at the seventh IHPBA world congress in 2008 and subsequently approved by the IHPBA Council. These define a minimum set of programme requirements for fellowships registered with IHPBA, intended for both programme directors and fellows, with an aim to equip trainees with the knowledge, clinical experience and technical skills required for independent HPB practice [19]. Further to this, a consensus conference on HPB training in North America was held in 2014, hosted by the Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society for Surgical Oncology (SSO), and the American Society of Transplantation Surgery (ASTS). This meeting sought to evaluate the current state of training in North America and reach consensus on programme requirements, minimum case volumes and quality metrics to prepare individuals for autonomous HPB practice and agree a framework for formative and summative assessment [20]. There is no pan-European training programme in surgical oncology, and no defined standards of training are stipulated by ESSO, however a core curriculum (basic and advanced) of knowledge expected of a surgical oncologist is set out by their Education and Training committee [21]. UEMS designate strict eligibility criteria for the European Board of Surgery Qualification.

5.2.1 Period of Training

IHPBA standards stipulate that a minimum of 12 continuous months of clinical training in the surgical management of HPB patients is required for accreditation in HPB surgery, or 24 months if both HPB and transplantation are pursued (although experience in transplantation is not mandatory) [19]. AHPBA and Complex General Surgical Oncology (CGSO) fellowships in North America similarly expect a minimum of 24 months of training [22]. The consensus and IHPBA recommendations emphasise the other ‘non-volumetric’ requirements of fellowship programmes; including exposure to the multi-disciplinary management of HPB disease, provision of an appropriate educational environment, adequate clinical content to meet the

needs of fellows without competition, an appropriate balance of service and education, access to a mentor and at least semi-annual appraisal of the fellow's progress with feedback [19].

5.2.2 Curriculum

Both IHPBA and UEMS provide a curriculum and syllabus to guide fellows through the essential areas of medical knowledge required to achieve expertise in HPB surgery [23, 24]. In the case of the European curriculum, this is intended to provide guidance to candidates intending to sit the European Board of Surgical Qualification (EBSQ), either as a Fellow of the European Board of Surgery in HPB or in Surgical Oncology—FEBS (HPB) or FEBS (SurgOnc). Eligibility for the UEMS examination is dependent on demonstration of board certification in the candidate's country of origin (which must be a member or associate member of UEMS), completion of a minimum of 2 years of HPB training after board certification, an accurate logbook of procedures with minimum numbers for accreditation and a minimum of one published peer reviewed paper as first, second or senior author in the field of HPB surgery. The IHPBA curriculum provides fellows with a framework for achieving an educational and training experience in preparation for independent HPB practice, as well a guide for programme directors to evaluate fellows' attainments.

The use of formative assessments ('in-training' tools to provide feedback and aid learning) to evaluate trainees' technical skills and surgical judgements varies enormously around the world [25]. In the UK, an online record, known as the Intercollegiate Surgical Curriculum Programme (ISCP), was introduced in 2008, where trainees are required to record a personal log of Workplace Based Assessments (WBAs) [26]. These incorporate the following domains: Procedural Based Assessments (PBAs) where feedback is given on technical operative skills; Case Based Discussions (CBDs) to allow reflection of patient cases and evaluate judgment and understanding of clinical scenarios; Clinical Evaluations (CEXs) where the trainee is directly observed in a clinical situation and Multi-Source Feedback (MSF) to provide the trainee with feedback from a range of assessors including consultants, trainees, nursing staff and other healthcare professionals.

In North America, The Milestone Project has been implemented with a similar purpose for General Surgery residents [27]. This model was discussed at the 2014 consensus conference as a reference framework for evaluating HPB fellows, with emphasis placed on the requirement of appropriate training of faculty to use such tools, as well as the need for trainees to trust the evaluation tool [20]. There is good evidence that such formative assessments enhance learning when used appropriately, especially in competency based training [28]. These tools should be used in the clinical environment in which the trainee works and applied regularly over time, so that feedback can be given longitudinally, and performance trends evaluated.

A distinction should be drawn between formative and summative assessments. Summative assessments seek to evaluate a trainee's performance at a particular

point in time against a pre-specified standard, and as such are not considered tools for learning [29]. Currently there is no specified requirement in any country for formalised summative assessment of HPB training above that required for General Surgery residents. The public therefore relies upon local hospital evaluation of individual candidates' breadth and depth of experience, as well as outcomes and performance, before recruitment into posts involving a complex HPB practice. The 2014 consensus agreed that a 'unified but flexible certificate process to recognise formal training in HPB surgery was desirable and worthy of exploration' [20]. Trainees in North America graduating from FC approved fellowships now receive an AHPBA certificate on completion of the programme and this process has proved to be competitive; with only 84% of fellows meeting the requirements between 2010 and 2014 [20].

5.3 Clinical Experience and Skills Acquisition

The Surgical Council on Resident Education (SCORE), a voluntary consortium of seven organisations involved in surgical residency training in the United States has defined competencies expected of a resident graduating in General Surgery [30]. Procedures are classified as *essential*, in which competency is required by the end of residency training, or *complex*, where generic experience is required but competency in specific procedures is not mandatory. No elective pancreatic procedures are included in the essential category; rather all are considered complex [11].

In the UK, trainees wishing to pursue a pancreatic practice 'declare' a special (or subspecialty) interest in Upper Gastrointestinal (GI) Surgery or Transplantation. Those selecting Upper GI have a requirement to complete a minimum of 35 'major Upper GI procedures' which includes pancreatic resection, before completion of general surgical training. In both countries therefore, it is highly likely that further training will be required before competency can be achieved in pancreatic surgery.

5.3.1 Volume and Training

The volume-outcome relationship is now well established in pancreatic surgery. It is clear that both hospital caseload and surgeon experience enhance survival outcomes in patients undergoing complex procedures including pancreatoduodenectomy [31]. Debate continues as to the case experience required to achieve proficiency and later expertise, but it has been suggested that acceptable operative morbidity can be observed following 20 pancreatoduodenectomies and mortality rates are comparable to an expert after 60 cases [31]. It is further recognised that the learning curve in surgical performance continues following completion of training; incremental increases in performance as measured by estimated blood loss, operative time and length of stay are observed in a surgeon's second 60 pancreatoduodenectomy

procedures compared to their first 60 cases [32]. Data would suggest that such case volume is achievable under the current model of HPB fellowship programmes; with a median of 40 pancreatoduodenectomies and 18 distal pancreatectomies accrued by Fellowship Council-approved fellows in the US [22]. IHPBA standards for training specify that programmes must guarantee a baseline minimum number of 30 pancreatic procedures per year as first surgeon in IHPBA accredited schemes [33].

5.3.2 Minimal Invasive HPB Surgery

The accrual of experience in minimally invasive HPB staging is required and that of minimally invasive surgical procedures is highly desirable, as highlighted by both IHPBA standards for training and the North America consensus statement [20, 34]. The integration of new technologies including robotics will be variable given the heterogeneity of fellowship programmes (e.g. transplantation linked schemes versus HPB specific schemes) but is viewed as an essential part of the evolution in the field. The low volume of many institutions means that proficiency requires the adoption of innovative training methods including virtual reality simulation, biotissue curriculum, video library training, intraoperative evaluation, video review and skill maintenance with ongoing assessment, so that a significant period of training occurs prior to the operating room [35, 36]. The majority of trainees currently entering fellowship positions have little to no robotic experience [37], however survey data indicates that the majority of HPB fellows desire more exposure to minimally invasive procedures [38]. Heterogeneity in experience is likely related to variation in the practice of training faculty. Designing a structured minimally-invasive curriculum could aid formalisation of such training and ensure operative exposure to such cases is sufficient to complete learning curves and achieve accredited safe practice where case volume allows [36]. The importance of addressing the need for such an objective curriculum is highlighted by survey data from practising pancreatic surgeons who cite the lack of adequate training as the principal barrier to the expansion of a laparoscopic pancreatic practice [39].

5.3.3 Human Factors

The evidence to support the influence of human factors on patient outcomes is now widely accepted [40]. Excellence in surgery has been described as not error-free performance, but rather the ability to manage error and problematic events during an operation [41]. Historically, the skills to manage such influences have not been formally taught in a structured way. The University of Aberdeen in collaboration with the Royal College of Surgeons of Edinburgh (RCSEd) has developed a structured method for the assessment of a surgeon's 'Non-Technical Skills in Surgery' (NOTSS), designed to rate four key domains: Situational Awareness, Decision

Making, Communication & Teamwork and Leadership [42]. Although few data currently exist on the specific application or validation of NOTSS in pancreatic surgery, such complex procedures are frequently performed by high performance surgical teams who are likely to observe improved patient outcomes from such self-reflection [43].

5.4 Research

Neither prior research experience or possession of a higher degree are required for entry to IHPBA, FC, SSO or ASTS fellowship schemes, although data exist in non-HPB specialties that pursuit of research during residency is associated with an increased likelihood of obtaining a competitive fellowship [44]. It is expected that IHPBA fellows initiate or participate in an investigative project during the 12-month fellowship and that presentation and peer reviewed publication of at least one such project is expected. Laboratory based research is optional but should be encouraged if desired by the fellow. The training centre is expected to provide a course on clinical research in human subjects and provide training in the methodology of conducting clinical trials, including biostatistics, research design and the ethics of human research [34].

5.5 Fellowship Satisfaction: The Trainee Experience

One AHPBA survey sampling views and attitudes of HPB surgeons (both in independent practice and in training) showed that the majority (67.5%) favoured a 2 year fellowship scheme and that just over half viewed a dedicated HPB route (rather than one affiliated to surgical oncology or transplantation) as the ideal pathway to autonomous HPB practice [45]. Other surveys comparing the trainee experience between the three routes to accreditation have highlighted other emergent trends of perceived differences: for example a reduced pancreas workload in transplant associated programmes, a greater overall operative exposure in AHPBA-FC accredited schemes and a desire for more exposure to benign pancreatic conditions, including pancreatitis, in SSO schemes [46]. In a group of AHPBA members, only 19% felt that too many HPB surgeons were being produced. A large proportion of respondents indicated that their preference was to combine practice with clinical or outcomes-based research and to undertake their career in a traditional academic environment [45].

Operative volume and variety appear to be the leading factors determining trainees' choice of fellowship programmes [37]. Certainly trainees who have undertaken a fellowship report higher volume annual practice for the benchmark operation of pancreatoduodenectomy than those who did not (high volume cut off being 20 cases per year) [47]. In terms of perceptions of required operative volumes for competent

independent practice in pancreatic surgery, these align in general with the operative numbers specified for fellowship completion by IHPBA, with a median of 29 cases for pancreatoduodenectomy. Most surgeons have exceeded this by the completion of training, achieving a median of 38 procedures [45]. Currently the majority of fellows do not expect to be fully trained in minimally invasive techniques by the completion of their fellowship [37]. Overall survey data suggests the majority of HPB fellows feel confident that they will be adequately prepared for autonomous practice by the end of their fellowship [37].

5.6 Technologies: Online Learning Platforms and Social Media

Recent years have seen a significant change to the way surgical training is delivered, with restricted hours and subspecialisation leading to an abandonment of the apprenticeship model and a shift in the balance between service-provision and educational opportunities [48, 49]. Alongside this have come technological developments that have responded to this reduced clinical exposure. Not only does this include the increasing use of technology by traditional surgical teaching methods, for example the use of online operative videos, but also includes access to online resources and distance learning programmes that seek to prepare trainees for postgraduate qualifications and even the award of a higher degree [50]. A number of such courses are now available, including those with HPB specific content, with an ever-expanding global reach and appeal. The initial evidence indicates that when used as a tool complementary to, rather than as a replacement for, the traditional surgical training model, these programmes enhance the attainment of surgeons in training [51]. Survey data suggests that smartphone applications already play a useful role in the education of pancreatic surgeons through the delivery of e-learning platforms, but also can be used as a mode of selecting advanced fellowship programmes [52].

Technology is being utilised in evermore innovative ways to disseminate research findings not only to the HPB community but also the general public. The use of visual abstracts on social media platforms such as Twitter has been shown to significantly enhance the engagement of healthcare professionals with research findings compared to the use of plain English abstracts or tweets alone [53]. Social media (SoMe) has not only become an instrument for connecting surgeons and driving forward movements and culture change, but also as a means of education and dissemination of research findings, for example the SoMe4HPB twitter account has 1766 followers at the time of writing (handle @hpb_so) and the use of twitter handles by journals (e.g. @hpbjournal) [54]. The surgical community is beginning to quantify the utility and influence that SoMe can have in training; for example a recent Twitter chat launched under the hashtag #SurgicalTraining amongst followers of the #SoMe4Surgery community, had a potential reach of 4,603,607 people [55]. The first shifts are being observed towards academic institutions using Social

Media 'Altmetrics' to evaluate academic outputs, although the full meaning and scope of how tweets, hashtags, impressions and 'likes' influence the impact and dissemination of research findings are still to be fully understood [56].

References

1. Sachs TE, Ejaz A, Weiss M, et al. Assessing the experience in complex hepatopancreatobiliary surgery among graduating chief residents: is the operative experience enough? Surgery. 2014;156(2):385–93.
2. Bell RH, Biester TW, Tabuenca A, et al. Operative experience of residents in US general surgery programs: a gap between expectation and experience. Ann Surg. 2009;249(5):719–24.
3. Cortez AR, Winer LK, Katsaros GD, et al. Resident operative experience in hepatopancreatobiliary surgery: exposing the divide. J Gastrointest Surg. 2020;24(4):796–803.
4. Robson AJ, Parks RW. HPB fellowship training: consensus and convergence. HPB (Oxford). 2016;18(5):397–9.
5. https://www.essoweb.org/mission-and-vision/.
6. D'Angelica MI, Chapman WC. HPB surgery: the specialty is here to stay, but the training is in evolution. Ann Surg Oncol. 2016;23(7):2123–5.
7. Altieri MS, Yang J, Yin D, et al. Presence of a fellowship improves perioperative outcomes following hepatopancreatobiliary procedures. Surg Endosc. 2017;31(7):2918–24.
8. McColl RJ, Shaheen AA, Brar B, et al. Survival after hepatic resection: impact of surgeon training on long-term outcome. Can J Surg. 2013;56(4):256–62.
9. Clark W, Hernandez J, McKeon BA, et al. Surgery residency training programmes have greater impact on outcomes after pancreaticoduodenectomy than hospital volume or surgeon frequency. HPB (Oxford). 2010;12(1):68–72.
10. Hammond Mobilio M, Brydges R, Patel P, et al. Struggles with autonomy: exploring the dual identities of surgeons and learners in the operating room. Am J Surg. 2020;219(2):233–9.
11. Zyromski NJ, Torbeck L, Canal DF, et al. Incorporating an HPB fellowship does not diminish surgical residents' HPB experience in a high-volume training centre. HPB (Oxford). 2010;12(2):123–8.
12. Rassadi R, Dickerman RM, Dunn EL, et al. Hepatopancreaticobiliary (HPB) surgery: what is the right fellowship for the right training? J Surg Educ. 2008;65(3):186–90.
13. Roberfroid D, Leonard C, Stordeur S. Physician supply forecast: better than peering in a crystal ball? Hum Resour Health. 2009;7:10.
14. Minter RM, Alseidi A, Hong JC, et al. Training in hepatopancreatobiliary surgery: assessment of the hepatopancreatobiliary surgery workforce in North America. Ann Surg. 2015;262(6):1065–70.
15. Scarborough JE, Pietrobon R, Bennett KM, et al. Workforce projections for hepato-pancreato-biliary surgery. J Am Coll Surg. 2008;206(4):678–84.
16. Edwards JP, Bressan A, Dharampal N, et al. Hepato-pancreato-biliary surgery workforce in Canada. Can J Surg. 2015;58(3):212–5.
17. Ali N, O'Rourke C, El-Hayek K, et al. Estimating the need for hepato-pancreatico-biliary surgeons in the USA. HPB (Oxford). 2015;17(4):352–6.
18. Pitt HA. International Hepato-Pancreato-Biliary Association: who are we and where are we going? HPB (Oxford). 2006;8(4):243–7.
19. Association EaTCftIH-P-B. Standards for hepato-pancreato-biliary training 2008. http://www.ihpba.org/assets/documents/hpb_training_standards.pdf. Accessed 27 Aug 2019.
20. Jeyarajah DR, Berman RS, Doyle M, et al. Consensus conference on North American training in hepatopancreaticobiliary surgery: a review of the conference and presentation of consensus statements. Ann Surg Oncol. 2016;23(7):2153–60.

21. Costa A, Van Hemelryck F, Aparicio A, et al. Continuing medical education in Europe: towards a harmonised system. Eur J Cancer. 2010;46(13):2340–3.
22. Jeyarajah DR, Patel S, Osman H. The current state of hepatopancreatobiliary fellowship experience in North America. J Surg Educ. 2015;72(1):144–7.
23. Committee EaT, Association IH-P-B. Curriculum for hepato-pancreato-biliary fellowships 2008. https://www.ihpba.org/media/hpb_curriculum.pdf. Accessed Oct 2019.
24. Section of Surgery and European Board of Surgery UEdMS. Syallabus UEMS-HPB surgery 2013. https://uemssurg.org/divisions/hpb-surgery/curriculum. Accessed Oct 2019.
25. Miller A, Archer J. Impact of workplace based assessment on doctors' education and performance: a systematic review. BMJ. 2010;341:c5064.
26. Beard JD. Assessment of surgical skills of trainees in the UK. Ann R Coll Surg Engl. 2008;90(4):282–5.
27. Cogbill TH, Malangoni MA, Potts JR, et al. The general surgery milestones project. J Am Coll Surg. 2014;218(5):1056–62.
28. Norcini J, Burch V. Workplace-based assessment as an educational tool: AMEE Guide No. 31. Med Teach. 2007;29(9):855–71.
29. Epstein RM. Assessment in medical education. N Engl J Med. 2007;356(4):387–96.
30. (SCORE) SCoRE. SCORE Curriculum Outline 2017–2018. http://www.absurgery.org/xfer/curriculumoutline2017-18.pdf. Accessed Oct 2019.
31. Schmidt CM, Turrini O, Parikh P, et al. Effect of hospital volume, surgeon experience, and surgeon volume on patient outcomes after pancreaticoduodenectomy: a single-institution experience. Arch Surg. 2010;145(7):634–40.
32. Tseng JF, Pisters PW, Lee JE, et al. The learning curve in pancreatic surgery. Surgery. 2007;141(5):694–701.
33. Raptis DA, Clavien PA, Committee IH-P-BAIEaT. Evaluation of Hepato-Pancreato-Biliary (HPB) fellowships: an international survey of programme directors. HPB (Oxford). 2011;13(4):279–85.
34. Education & Training Committee IH-P-BA. Standards for hepato-pancreato-biliary training 2008. http://www.ihpba.org/media/hpb_training_standards.pdf. Accessed Oct 2019.
35. Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami international evidence-based guidelines on minimally invasive pancreas resection. Ann Surg. 2020;271(1):1–14.
36. Hogg ME, Besselink MG, Clavien PA, et al. Training in minimally invasive pancreatic resections: a paradigm shift away from "see one, do one, teach one". HPB (Oxford). 2017;19(3):234–45.
37. Pagkratis S, Cho EE, Lewis F, et al. Expectations of hepato-pancreato-biliary fellows; do we meet them? J Surg Educ. 2019;76(6):1546–55.
38. Siddiqui IA, Sastry AV, Martinie JB, et al. Fellows' perspective of HPB training programs in North America: results of a survey. HPB (Oxford). 2018;20(8):695–701.
39. Jrearz R, Govindarajan A, Jayaraman S. A survey of current practices and barriers to expanding laparoscopic HPB surgery in Canada. HPB (Oxford). 2017;19(1):42–6.
40. Shouhed D, Gewertz B, Wiegmann D, et al. Integrating human factors research and surgery: a review. Arch Surg. 2012;147(12):1141–6.
41. de Leval MR, Carthey J, Wright DJ, et al. Human factors and cardiac surgery: a multicenter study. J Thorac Cardiovasc Surg. 2000;119(4 Pt 1):661–72.
42. Yule J, Hill K, Yule S. Development and evaluation of a patient-centred measurement tool for surgeons' non-technical skills. Br J Surg. 2018;105(7):876–84.
43. Jung JJ, Yule S, Boet S, et al. Nontechnical skill assessment of the collective surgical team using the non-technical skills for surgeons (NOTSS) system. Ann Surg. 2019.
44. Lessin MS, Klein MD. Does research during general surgery residency correlate with academic pursuits after pediatric surgery residency? J Pediatr Surg. 1995;30(9):1310–3.
45. Seshadri RM, Ali N, Warner S, et al. Training and practice of the next generation HPB surgeon: analysis of the 2014 AHPBA residents' and fellows' symposium survey. HPB (Oxford). 2015;17(12):1096–104.

46. Warner SG, Alseidi AA, Hong J, et al. What to expect when you're expecting a hepatopancreatobiliary surgeon: self-reported experiences of HPB surgeons from different training pathways. HPB (Oxford). 2015;17(9):785–90.
47. Kennedy GT, McMillan MT, Sprys MH, et al. The influence of fellowship training on the practice of pancreatoduodenectomy. HPB (Oxford). 2016;18(12):965–78.
48. Health GBDo. Protecting staff; delivering services: implementing the European working time directive for doctors in training. London; 2003. p. 1–3.
49. Rybock JD. Residents' duty hours and professionalism. N Engl J Med. 2009;361(9):930–1.
50. Aryal KR, Pereira J. E learning in surgery. Indian J Surg. 2014;76(6):487–93.
51. Smith PJ, Wigmore SJ, Paisley A, et al. Distance learning improves attainment of professional milestones in the early years of surgical training. Ann Surg. 2013;258(5):838–42; discussion 842–3.
52. Roy M, Dip F, Rosales A, et al. Smartphone application as an education platform in hepatopancreato-biliary surgery. Surg Innov. 2019;26(5):613–20.
53. Chapman SJ, Grossman RC, FitzPatrick MEB, et al. Randomized controlled trial of plain English and visual abstracts for disseminating surgical research via social media. Br J Surg. 2019;106:1611–6.
54. Søreide K, Mackenzie G, Polom K, et al. Tweeting the meeting: quantitative and qualitative twitter activity during the 38th ESSO conference. Eur J Surg Oncol. 2019;45(2):284–9.
55. Gallo G, Sturiale A, De Simone V, et al. Epistemic networks on twitter: a new way to learn. J Invest Surg. 2019;1–9. https://doi.org/10.1080/08941939.2019.1656787.
56. Díaz-Faes AA, Bowman TD, Costas R. Towards a second generation of 'social media metrics': characterizing twitter communities of attention around science. PLoS One. 2019;14(5):e0216408.

Chapter 6
Quality of Care Indicators in Pancreatic Cancer

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Take Home Messages

- Establishing rigorous and disciplined measures of quality are a critical step in evaluating quality of care for patients diagnosed with pancreatic cancer.
- The measures or quality indicators should evaluate all facets of the disease trajectory, namely diagnosis and staging, surgery, other treatment, patient management and outcomes, within the framework of a continuous improvement cycle.
- Clinical measures often do not take into account a patient's wellbeing, functional status and health-related quality of life. These are best evaluated using patient-reported outcome measures.

Pearls and Pitfalls

- The measurement of quality is hampered by inadequate data sources, a lack of systematic outcome assessment, suboptimal documentation of care delivery and a lack of formal monitoring systems.

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- Escalating costs of health care coupled with increased burden on financial and human resources is a barrier to quality improvement.
- The current model of healthcare delivery has led to a siloed speciality-driven approach with the potential to game the system, slow progress in performance improvement and is projected to be unsustainable in the near future.

Future Perspectives
- Quality of Care indicators will play a pivotal role in establishing a value-based healthcare delivery system that measures and manages patient level costs over complete cycles of care.

6.1 Introduction

There has been a shift in our understanding and evaluation of quality of care in the past few decades, driven by maestros who dedicated their lives to improvement sciences. The conversation has moved from achieving not only improved clinical outcomes but also to understanding 'what matters to patients'. In pancreatic cancer, which is often classified as a low survival cancer, optimised care can improve survival and quality of life. Measurement from a clinical and patient perspective using well developed quality indicators is critical in evaluating variations in care and identifying areas for improvement.

6.2 Defining Quality of Care

The measurement of quality to improve health care is complex with no single, precise or ideal definition of quality. The definition of quality as it is best known is captured in Box 6.1.

Box 6.1 Defining Quality
In 1990, the Institute of Medicine (IOM) Committee compiled, analysed and debated on the many available definitions. The committee's final definition is outlined as follows:

> "*Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.*" [1]

Quality of care is best viewed in terms of performance on a range of dimensions as further defined by the Institute of Medicine (safe, effective, efficient, timely, patient-centred and equitable care) and the components of health care (structure, process, outcome) described by Donabedian [2, 3].

Structures measure the foundation on which a service is built. For example, the services it provides and the governance structure in place. Without strong foundations health systems are unable to safely, and effectively deliver care, which is equitable, timely and patient-centred.

Processes of care are those interventions which are highly correlated with better health outcomes for patients. For example, there is strong evidence that surgical antibiotic prophylaxis administered within two hours prior to incision, according to the type of operation will reduce risk of post-operative infection [4]. Processes of care can often be extracted from administrative datasets or collected through audit with relative ease.

Outcomes of care are arguably the most important means of measuring the quality of care provided by health services. However, there are complexities in measuring outcomes which are not as clear cut as when assessing either structures or processes of care. For example, choosing the time point to measure an outcome is important; too early after the care may not have provided sufficient time for the effect to be realised. Outcomes measured some time after an episode of care may be impacted by other factors aside from the treatment which was delivered [5]. For this reason, outcomes require careful deliberations. Risk adjustment is also essential in order to be certain that patients' outcomes are being adjusted for variables that are not related to the delivery of health care, e.g. age or comorbidities [6].

The conceptual framework that underpins the evaluation of quality care is presented in Fig. 6.1.

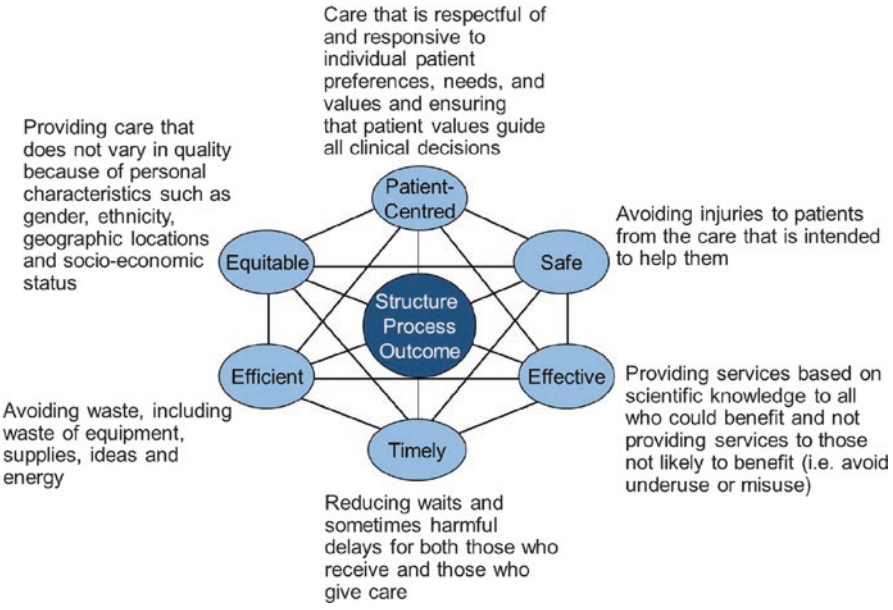

Fig. 6.1 Conceptual framework that underpins the quality of care

6.3 Variations in Quality of Care

To understand quality in pancreatic cancer and the variations that exist to achieve optimal care, we have to first ask the question, 'what is good quality of care'? This is explored using examples relating to care of patients with pancreatic cancer and applying the aforementioned dimensions of quality in Box 6.2.

Box 6.2 Exemplars of Variations in Care in Pancreatic Cancer

Is care safe? There is accumulating evidence that patients undergoing pancreaticoduodenectomy in hospitals managing low volumes of patients have higher mortality rates than those treating high volumes of patients with pancreatic cancer [7, 8]. This is likely the result of increased ability to deliver safe care in hospitals resourced to manage these complex patients. As a result of this evidence, a call has recently been made in a number of United States (US) health services to limit pancreatic surgery privileges to surgeons performing at least five cases per year and facilities with at least 20 cases per year [9]. In addition to using mortality to assess safety of care, other markers of unsafe care include iatrogenic injuries and complications such as infection, haemorrhage, pressure ulcers, drug errors, and wound dehiscence.
Is care effective? There are cases where planned procedures (e.g. diagnostic laparoscopy) or a planned surgery for potentially resectable disease is abandoned intraoperatively. An abandoned surgery may indicate that the patient has not been effectively staged. In addition, surgery should ideally result in clear margins (margin-negative or R0). Unfortunately, around 20% of cases have microscopically positive (R1) or macroscopically positive (R2) margins resulting in poorer clinical outcomes [10]. R1 margins may be a marker of ineffective pre-operative staging before undertaking surgery.
Is care timely? Pancreatic cancer is an aggressive disease with majority of patients diagnosed at an advanced stage. The pathway to early diagnosis is complicated by the onset of generalised gastrointestinal symptoms, comorbidities and delays in referral. Patients can experience significant delays from referral to diagnosis when undergoing investigations for generalised gastrointestinal symptoms with a median delay of 64.5 days [11].
Is care equitable? Differences in complications and mortality may be due to disparity in quality of care provided by individual providers or institutions. We know that people living in regional or rural locations can be less likely than their city counterparts to receive anti-cancer therapy [12]. Patients living in areas with higher socio-economic status are also more likely to receive access to more advanced medical care that is associated with improved survival and improved quality of life [13].
Is care efficient? Structured reporting of surgical pathology increases the accuracy, accessibility, completeness and uniformity of surgical pathology diagnosis. However, there is variable quality of pathological reporting with some evidence that up to 44% of free text reports do not contain sufficient information for disease stage to be inferred. In one study margin status was recorded in only 11% of reports [14].
Is care patient-centred? Current expert opinion and international recommendations state that management decisions, certainly for early pancreatic cancer should be made within the framework of a multidisciplinary team (MDT) meeting to ensure that the full range of available and appropriate treatment options are considered [15]. Yet, only a third of patients diagnosed with pancreatic cancer are presented to MDT meetings [13].

To understand the reasons behind variations in care, evaluating the quality of care delivered to patients diagnosed with pancreatic cancer is an essential step.

6.4 Monitoring Quality of Care

The measurement of quality of care for patients diagnosed with pancreatic cancer across the trajectory of the disease requires an understanding of scientific principles to underpin our measurement tools to obtain reliable and comparable data. Sources of data for quality assessment can include direct observation of a health care encounter, medical records, administrative databases, incident reports, clinical registries, patient satisfaction and patient experience surveys. Currently, the measurement of quality is hampered by inadequate data sources, a lack of systematic outcome assessment, suboptimal documentation of care delivery and a lack of formal monitoring systems [16]. A persisting challenge in measuring quality is ensuring that metrics used are reliable and reproducible. A high level of scientific credibility from measurement tools and data sources is demanded.

6.4.1 Clinical Indicators

Clinical indicators provide the basis for evaluation of care in pancreatic cancer. They quantitatively measure aspects of the structure, process and outcomes of patient care to act as a 'flag' that indicate areas for further investigation [16].

Clinical indicators can be used as a basis for self-improvement to inform policy and strategy making, to monitor performance of services and of funding bodies, to empower consumers to help make decisions about their choice of health services and to identify poor performance. Increasingly they are providing the basis for financial incentives related to select health service parameters [17].

Clinical indicators, in and of themselves, are ineffective unless incorporated into a quality improvement cycle.

Box 6.3 The Father of Quality
Edward Deming developed such an approach in the manufacturing industry post the second World War in Japan, and it has since been widely implemented in health service delivery [18]. Considered the Father of Quality, Deming introduced the Total Quality Management paradigm, which promoted systematic analysis and measurement of processes linked to producing quality outputs.

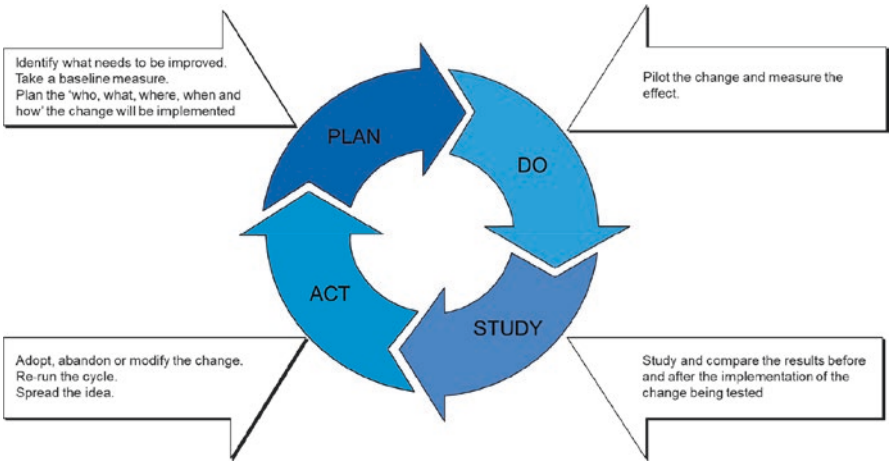

Fig. 6.2 Plan-Do-Study-Act cycle and model for improvement [19]

The Deming continuous quality improvement cycle ensured that on an ongoing basis opportunities to improve were harnessed. The Deming Cycle, also referred to as the Plan-Do-Study-Act cycle, or the Plan-Do-Check-Act (Fig. 6.2).

6.4.2 Development and Implementation of Clinical Quality Indicators in Pancreatic Cancer

Clinical indicators for pancreatic cancer care should include all facets of the disease trajectory, namely *diagnosis and staging, surgery, other treatment, patient management* and *outcomes.* They can be derived from academic literature or, where scientific evidence is lacking, determined by an expert panel of health professionals in a consensus process [16]. The most widely used consensus method is the Delphi technique initially developed in 1969. The Delphi method includes questionnaires or surveys to determine the most appropriate indicators from a panel of experts [20]. More recently, a modified Delphi method was introduced which includes an initial survey followed by the panel meeting face to face to discuss the results of the first survey round, focussing on areas of disagreement and the opportunity to modify the original list of proposed indicators. Other consensus methods include the Nominal Group Technique which is a structured process and requires participants to brainstorm ideas followed by a discussion and ranking of an item's importance [21]. Figure 6.3 *provides a schematic outlining the processes in the development of clinical indicators. Step 1* summarises the development of a core set of quality indicators; *Step 2* discusses how to monitor and analyse the data, and *Step 3* describes the processes for implementation and review (Fig. 6.3).

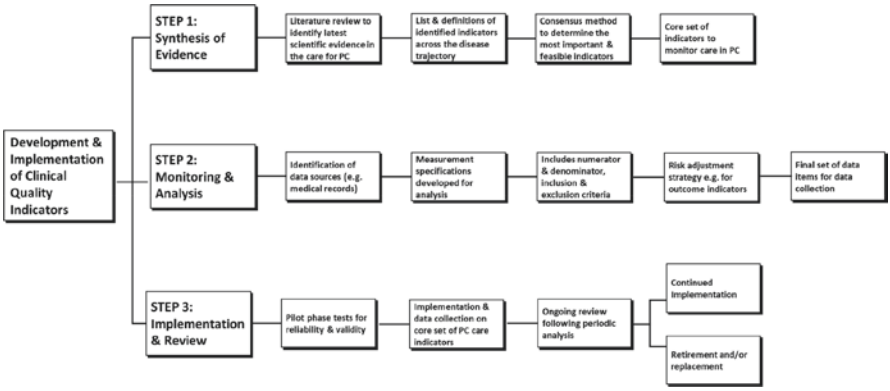

Fig. 6.3 Steps to developing clinical quality of care indicators for pancreatic cancer. (Adapted from Fitch et al. & Prosser-Snelling E, Morris E [17, 21])

6.4.2.1 Step 1: Synthesis of Evidence

In 2009, Bilimoria and colleagues identified a set of surgical quality indicators for pancreatic cancer. This was subsequently built upon by Burmeister and colleagues in 2016, who identified a set of care statements that included patient management indicators [22, 23]. Further to this work, the authors of this chapter developed, through a modified Delphi approach, a core set of 27 clinical quality indicators to monitor care across all areas of the disease trajectory (*seven* diagnosis and staging, *five* surgical, *four* other treatment, *five* patient management and *six* outcome measures) as listed in Table 6.1 [24].

6.4.2.2 Step 2: Monitoring and Analysis

Once a core set of clinical quality indicators to monitor care in pancreatic cancer has been established via a consensus method, the next phase (Fig. 6.3, *step 2*) is to determine the data sources from which data will be collected such as administrative data or medical record review. Measurement specifications include determining the numerator, denominator, inclusion and exclusion criteria for each clinical quality indicator. A risk adjustment and risk stratification approach may be required, particularly if the indicator is assessing a health outcome which may be impacted by factors other than those within the capacity of the health service to control. Risk adjustment may be used to introduce a weighted approach to consider the impact of major confounders impacting the outcome. These are commonly the patient's age and stage of disease at the time when the indicator is being measured. Risk stratification may involve measuring the indicator in a particular subset of the population of patients with pancreatic cancer; for example only those with stage I disease undergoing surgery.

Table 6.1 Core set of pancreatic cancer indicators developed through a modified Delphi approach [24]

Indicators
Diagnosis and staging
Documented pancreatic protocol CT or MRI scan for diagnosis and/or staging
Tissue biopsy attempted prior to chemotherapy or radiotherapy
Documented baseline CA19-9 level before treatment
Documented ECOG and/or ASA at presentation
Time from referral to definitive treatment within 60 days (relief of biliary obstruction is not definitive treatment)
MRI, CT or PET completed following neoadjuvant treatment
Operability of tumour is clearly defined and documented as either operable/resectable, borderline resectable, locally advanced (unresectable) or metastatic (unresectable)
Surgery
Royal College of Pathologists of Australasia or equivalent reporting system used to document findings for patients undergoing surgical resection
Standard lymphadenectomy with the removal of ≥10 lymph nodes pathologically examined and documented
"Number of R1 resections (positive ≤1 mm margin) for those that have a synoptic report or Number of R1 resections (positive ≤1 mm margin) for those that do not have a synoptic report"
Number of patients undergoing pancreatic cancer surgery in a level 1–4 hospital
All patients who did not undergo surgery should have a valid reason documented
Other treatment
Adjuvant chemotherapy administered following surgery or a reason documented for not undergoing treatment
Chemotherapy ± chemo-radiation offered to patients with locally advanced disease, or a reason documented for not undergoing treatment
Neo-adjuvant chemotherapy ± chemo-radiation offered to patients with borderline resectable disease, or a valid reason documented for not undergoing treatment
Number of patients who saw a medical or radiation oncologist or a reason documented for not doing so
Patient management
Disease management for all patients discussed at a MDT meeting
Number of patients with biliary obstruction managed surgically or by stent
All patients with metastatic disease referred to (or seen by) palliative care specialist
All patients having completed treatment followed up specialist every 3–6 months for up to 2 years
Number of patients included in a clinical trial
Outcome
Patients requiring a re-operation following surgical resection
Patient died within 30-days of last dose of chemotherapy
>2 ED presentations in the last 30-days before death
2 year and 5 year survival rates for patients who underwent a surgical resection
≥14 days in acute hospital
30-day and 90-day mortality rate following surgical resection

It is also important to consider how data will be collected and by whom. Data can be collected by clinicians or trained data collectors. Ideally, the person collecting the data for quality indicators should be impartial and independent to avoid any potential biases in recruitment or data collection. An important consideration is where the data will be stored. Electronic databases such as REDCap (Research Electronic Data Capture) provide a secure, web-based software platform designed to support data capture and storage [25].

6.4.2.3 Step 3: Implementation and Review

Following the development of key data items for collection of relevant information, implementation should begin with a pilot phase to test the reliability and validity of the data items. This can be dependent on the accuracy of the coding and recording of data if using an administrative data source, and data completeness for other sources such as medical chart review [26]. Figure 6.3, *step 3* outlines the lifecycle of a clinical quality indicator. Following implementation of the core set, periodic analysis and evaluation is necessary not only for feedback and reporting but also for quality assurance that each indicator is continually measuring 'what it is meant to measure'. With time some clinical quality indicators may become obsolete due to the changing landscape of evidence and others may become appropriate if sufficient evidence has accumulated to deem it quality care. For example, the administration of neo-adjuvant therapy in *resectable* pancreatic cancer is yet to be established as best practice, although it has gained momentum as standard of care for other gastrointestinal cancers [27].

6.4.3 Value-Based Health Care

The escalating costs of health care, due in part to expensive new technology and drugs, coupled with increased burden on financial and human resources is a barrier to quality improvement. Health care expenditure continues to increase across many countries at a rate above that of inflation. The current model of health care delivery in many countries provides care in a fee-for-service approach often focusing solely on service volume. Costing systems are organised by spending category such as employee costs, equipment, devices, imaging, laboratory tests, and pharmaceuticals. This model has led to a siloed speciality-driven approach with the potential to game the system, slow progress in performance improvement and is projected to be unsustainable in the near future. The alternative proposal is an overhaul of the current system to introduce value-based health care delivery, a model that measures and manages patient level costs over complete cycles of care for a variety of medical conditions [28].

Of a particular note, is the importance of assessing clinical measures such as complications and survival as well as patient-reported outcomes (PROs).

Value-based care can be conceptualised by the following formula in Fig. 6.4 [29]:

Michael Porter first introduced the concept of value-based health care in an article published in the New England Journal of Medicine in 2009 [29]. In this article, Porter espouses that to achieve a value-based delivery system the following steps are required:

1. Measure and disseminate health outcomes for every provider and every medical condition. Outcomes must be measured over the full cycle of care from diagnosis through to treatment and recovery or end-of-life. The degree of health prior to treatment should be considered when assessing outcomes following diagnosis and treatment. Outcomes should assess the quality of health and recovery achieved, time required for recovery, patient discomfort and sustainability of recovery.
2. Re-examine how prevention, wellness, screening and routine health services are delivered. There is a need to invest where required to defined patient populations with unified reimbursement.
3. Reorganise care around medical conditions or sets of closely related conditions
4. Reimbursement should align everyone's interests around improving value for patients. Bundled payments to cover the entire cycle of care for a medical condition will shift the focus towards restoring function and maintaining health.
5. Providers should compete for patients, based on value at the medical-condition level. This will foster excellent providers.
6. Electronic medical records will enable value improvement if they support integrated care and outcome measurement.
7. Consumers must engage in their health and in health care. They must take responsibility for their health.

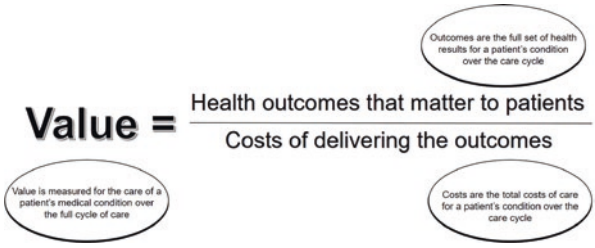

Fig. 6.4 Value-based health care delivery

6.4.4 Patient-Reported Outcome Measures (PROMs) in Pancreatic Cancer

When discussing clinical indicators earlier in this chapter, the objective was to determine from clinicians or experts in the field of pancreatic cancer, the most important and feasible measures to monitor clinical outcomes. However, clinical measures often do not take into account a patient's wellbeing, functional status and health-related quality of life. Further, the views on 'what matters' to a patient may differ to that of a clinician. For example, in one study, clinicians placed higher importance on symptoms such as pain, nausea, vomiting, abdominal complaints, itching and jaundice compared to patients in a palliative setting [30]. Which leads us to the question, how do we determine the health outcomes that matter most to patients diagnosed with pancreatic cancer?

Pancreatic cancer is characterised by poor survival, high symptom and psychological burden and as described by one study, 'a tsunami of unmet needs' [31, 32]. Integration of PROs into clinical practice, health service or health systems level using structured instruments (e.g. standardised questionnaires) known as Patient-Reported Outcome Measures (PROMs) have shown to improve patient-clinician communication, overall patient care and outcomes [33].

There has been an exponential rise in the number of PROMs developed for cancer care over the past three decades. Given the considerable burden of this disease and poor survival, it is especially important that the selected PROM has undergone psychometric evaluation in a pancreatic cancer population and is deemed reliable, valid and sensitive to change, rather than merely extrapolated from other populations. Following an extensive and detailed systematic review, we recommend one of three multidimensional PROMs be used depending on the intent: FACT-HEP in patients with unresectable pancreatic cancer; QLQ-PAN26 (in conjunction with its core QLQ-C30 PROM) in those with resectable pancreatic cancer; and MDASI-GI, a tool that may be useful irrespective of disease stage [34].

6.4.5 Evaluating Quality of Care

Establishing and evaluating rigorous and disciplined measures of quality are a critical step in evaluating quality of care. We have demonstrated that the comprehensive evaluation of quality of care in pancreatic cancer requires a two-fold approach based on clinical quality indicators and PROMs. In addition, the evaluation of outcome measures at the patient-level can estimate value in health care delivery that is patient-centric.

Several authors have now used this approach to evaluate quality of care in defined populations of patients with pancreatic cancer. Bilimoria and colleagues demonstrated variability in the surgical quality of care in pancreatic cancer. Adherence to individual level indicators ranged from 49.6 to 97.2% and

hospital-level indicators ranged from 6.8 to 99.9% [22]. Burmeister and colleagues were able to demonstrate significant disparities based on socio-economic status. Further, not all patients were presented to MDTs (31%), received psychosocial support (19%), participated in clinical trials (7%), or were first seen by a hepatobiliary surgeon (19%) [13].

There has been continued efforts to develop and standardise core clinical and patient-reported indicators but a significant gap remains in the literature on the evaluation of quality of care for patients diagnosed with pancreatic cancer.

6.5 Feedback and Reporting

The development and implementation of quality indicators requires detailed synthesis and evaluation, with good access to population health and statistical resources [17]. Increasing attention is being paid to the importance of using state-wide or national clinical quality registries to monitor, benchmark, and report risk-adjusted data on quality of care. Clinical quality registries have shown to drive continuous improvement by using a feedback mechanism to report on the appropriateness of care (process) and the effectiveness of care (outcomes). They also generate more reliable and credible information compared to administrative databases [35]. Examples of clinical quality registries that exist for pancreatic cancer are the Pancreatic Cancer Collaborative Registry [36], Danish Pancreatic Cancer Database [37], and the Upper Gastrointestinal Registry (UGICR) which has a module dedicated to pancreatic cancer [38]. Regardless of whether data for clinical indicators or PROMs are supported by a clinical registry, feedback provided through timely reporting, quality indicators can be effective in improving professional practice [39].

6.6 Examining Variation

Inevitably, when examining quality of care using quality indicators, sub-optimal performance will be identified. We have discussed the need to incorporate quality indicators in a continuous improvement cycle, but how do we identify what needs to be done in order to improve? Often this requires a deep understanding of the variation identified. There are many factors which impact best practice that hasn't been identified. Understanding this is pivotal when developing the improvement cycle.

One patient management indicator developed as part of the core set (Table 6.1) is '*disease management for all patients discussed in a MDT meeting*'. Data from the UGICR show that approximately 30% of patients are not discussed at MDT meetings, the majority (67%) of which are those with metastatic disease. Although 90% of patients undergoing a surgical resection are discussed at MDT meetings, 27% are discussed following their surgery rather than prior to treatment. A qualitative approach such as interviews or focus groups may be necessary to identify the

barriers and enablers impacting on health professionals involved in patient care, in order to facilitate quality improvement and optimise performance measured through this indicator.

6.7 Conclusions

In this chapter, we have introduced a conceptual framework to consider when introducing a system to monitor quality of care in patients with pancreatic cancer. We have outlined clinical indicators selected by an expert panel to measure quality of care and discussed the need to incorporate measurement within a continuous quality improvement cycle, in which data are constantly being examined and improvement sought. We have discussed value-based health care and describe why it is an important societal consideration when examining quality of care. Finally, we provide some models to help understand variation in quality of care.

References

1. Institute of Medicine (US) Committee to Design a Strategy for Quality Review and Assurance in Medicare. Chapter 5, Defining quality of care. In: Medicare: a strategy for quality assurance, vol. II. Sources and methods. Washington, DC: National Academies Press (US); 1990.
2. Institute of Medicine Committee on Quality of Health Care in A. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press (US) . Copyright 2001 by the National Academy of Sciences. All rights reserved.; 2001.
3. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q. 1966;44(3 Suppl):166–206.
4. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of duration and type of surgical prophylaxis with antimicrobial-associated adverse events. JAMA Surg. 2019;154(7):590–8.
5. Coster WJ. Making the best match: selecting outcome measures for clinical trials and outcome studies. Am J Occup Ther. 2013;67(2):162–70.
6. Lane-Fall MB, Neuman MD. Outcomes measures and risk adjustment. Int Anesthesiol Clin. 2013;51(4):10–21.
7. Kutlu OC, Lee JE, Katz MH, Tzeng CD, Wolff RA, Varadhachary GR, et al. Open pancreaticoduodenectomy case volume predicts outcome of laparoscopic approach: a population-based analysis. Ann Surg. 2018;267(3):552–60.
8. Gooiker GA, van Gijn W, Wouters MW, Post PN, van de Velde CJ, Tollenaar RA. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg. 2011;98(4):485–94.
9. Urbach DR. Pledging to eliminate low-volume surgery. N Engl J Med. 2015;373(15):1388–90.
10. Torgeson A, Garrido-Laguna I, Tao R, Cannon GM, Scaife CL, Lloyd S. Value of surgical resection and timing of therapy in patients with pancreatic cancer at high risk for positive margins. ESMO Open. 2018;3(1):e000282.
11. Apollos JR, Sami S, Prasanth MN, Jeyakumar J, McFadyen AK. Pre-diagnostic delays caused by gastrointestinal investigations do not affect outcomes in pancreatic cancer. Ann Med Surg. 2018;34:66–70.

12. Martin HL, Ohara K, Chin W, Davidson A, Bayliss E, Redfern A, et al. Cancer services in Western Australia: a comparison of regional outcomes with metropolitan Perth. Aust J Rural Health. 2015;23(5):302–8.
13. Burmeister EA, O'Connell DL, Jordan SJ, Goldstein D, Merrett N, Wyld DK, et al. Factors associated with quality of care for patients with pancreatic cancer in Australia. Med J Aust. 2016;205(10):459–65.
14. Gill AJ, Johns AL, Eckstein R, Samra JS, Kaufman A, Chang DK, et al. Synoptic reporting improves histopathological assessment of pancreatic resection specimens. Pathology. 2009;41(2):161–7.
15. Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Policy. 2015;119(4):464–74.
16. Mainz J. Defining and classifying clinical indicators for quality improvement. Int J Qual Health Care. 2003;15(6):523–30.
17. Prosser-Snelling E, Morris E. Quality indicators. Obstetr Gynaecol Reprod Med. 2017;27(9):290–2.
18. Deming WE. Out of the crisis. Cambridge, MA: MIT Press; 2000.
19. Taylor MJ, McNicholas C, Nicolay C, Darzi A, Bell D, Reed JE. Systematic review of the application of the plan–do–study–act method to improve quality in healthcare. BMJ Qual Saf. 2014;23(4):290.
20. Dalkey NC. The Delphi method: an experimental study of group opinion. Santa Monica, CA: RAND Corp; 1969.
21. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR. The RAND/UCLA appropriateness method user's manual. Santa Monica, CA: RAND Corp; 2001.
22. Bilimoria KY, Bentrem DJ, Lillemoe KD, Talamonti MS, Ko CY, On behalf of the American College of Surgeons' Pancreatic Cancer Quality Indicator Development Expert P. Assessment of pancreatic cancer care in the United States based on formally developed quality indicators. J Natl Cancer Inst. 2009;101(12):848–59.
23. Burmeister EA, Jordan SJ, O'Connell DL, Beesley VL, Goldstein D, Gooden HM, et al. Using a Delphi process to determine optimal care for patients with pancreatic cancer. Asia Pac J Clin Oncol. 2016;12(2):105–14.
24. Maharaj AD, Ioannou L, Croagh D, Zalcberg J, Neale RE, Goldstein D, et al. Monitoring quality of care for patients with pancreatic cancer: a modified Delphi consensus. HPB (Oxford). 2019;21(4):444–55.
25. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
26. Corbellini C, Andreoni B, Ansaloni L, Sgroi G, Martinotti M, Scandroglio I, et al. Reliability and validity assessment of administrative databases in measuring the quality of rectal cancer management. Tumori J. 2018;104(1):51–9.
27. Lordick F, On behalf of the EGC, Mariette C, On behalf of the EGC, Haustermans K, On behalf of the EGC, et al. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2016;27(Suppl 5):v50–7.
28. Porter ME, Kaplan RS, Frigo ML. Managing healthcare costs and value. Strategic Finance. 2017;98(7):24.
29. Porter ME. What is value in health care? N Engl J Med. 2010;363(26):2477–81.
30. Gerritsen A, Jacobs M, Henselmans I, van Hattum J, Efficace F, Creemers G-J, et al. Developing a core set of patient-reported outcomes in pancreatic cancer: a Delphi survey. Eur J Cancer. 2016;57:68–77.
31. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10–27.

32. Beesley VL, Janda M, Goldstein D, Gooden H, Merrett ND, O'Connell DL, et al. A tsunami of unmet needs: pancreatic and ampullary cancer patients' supportive care needs and use of community and allied health services. Psychooncology. 2016;25(2):150–7.
33. Snyder CF, Aaronson NK, Choucair AK, Elliott TE, Greenhalgh J, Halyard MY, et al. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. Qual Life Res. 2012;21(8):1305–14.
34. Maharaj AD, Samoborec S, Evans SM, Zalcberg J, Neale RE, Goldstein D, Merrett N, White K, Croagh D, Pilgrim CHC, Evans P, Knowles B, Leong T, Philip J, Smith M, Ioannou L. Patient-reported outcome measures (PROMs) in pancreatic cancer: a systematic review. HPB (Oxford). 2019;22(2):187–203.
35. Wilcox N, McNeil JJ. Clinical quality registries have the potential to drive improvements in the appropriateness of care. Med J Aust. 2016;205(S10):S21–S6.
36. Sherman S, Shats O, Ketcham MA, Anderson MA, Whitcomb DC, Lynch HT, et al. PCCR: pancreatic cancer collaborative registry. Cancer Informat. 2011;10:83–91.
37. Fristrup C, Detlefsen S, Hansen CP, Ladekarl M. Danish pancreatic cancer database. Clin Epidemiol. 2016;8:645–8.
38. Maharaj AD, Holland JF, Scarborough R, Evans SM, Ioannou L, Brown WA, Croagh D, Pilgrim CHC, Kench JG, Lipton LR, Leong T, McNeil JJ, Nikfarjam M, Aly A, Burton PR, Cashin PA, Chu J, Duong C, Evans P, Goldstein D, Haydon A, Hii MW, Knowles BPF, Merrett N, Michael M, Neale RE, Philip J, Porter IWT, Smith M, Spillane J, Tagkalidis PP, Zalcberg J. Upper Gastrointestinal Cancer Registry (UGICR): a clinical quality registry to monitor and improve care in upper gastrointestinal cancers. BMJ Open. 2019;9(9):e031434.
39. Ivers N, Jamtvedt G, Flottorp S, Young JM, Odgaard-Jensen J, French SD, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012;(6):CD000259.

Chapter 7
The Quantity and Quality of Surgical Trials in Pancreatic Cancer

Felix J. Hüttner, Pascal Probst, and Markus K. Diener

Take Home Messages
- Quantity and quality of surgical trials in pancreatic cancer have increased.
- Evidence gaps remain for several issues.
- Research prioritization and collaboration are needed to answer the most relevant questions in a timely manner.

Pearls and Pitfalls

Pearls
- The annual and decadal output of surgical trials on pancreatic malignancy increased approximately fourfold over the last three decades.
- The number of trials with low risk of bias demonstrated a substantial increase during the last decade for nearly all domains of the Cochrane Risk of Bias Tool.

Pitfalls
- Surgical procedures apart from partial pancreatoduodenectomy such as e.g. distal pancreatectomy are underrepresented in the current body of evidence.

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- A relevant proportion of trials are limited by small sample sizes and short follow-up durations.
- For specific domains of bias such as blinding and selective reporting, still only approximately one quarter of trials was at low risk of bias during the last decade.

Future Perspectives
To close the most important remaining evidence gaps in a prioritized fashion, relevant stakeholders should join forces to conduct collaborative surgical trials. Despite national initiatives in individual countries, international organizations such as the European Society of Surgical Oncology or the European-African or International Hepato-Pancreato-Biliary Associations could be key players in this process.

7.1 Introduction

Surgical research is associated with specific challenges, such as influence of learning curves, intricate blinding, or ethical issues with placebo controls or sham surgery [1–4]. Therefore, the number of surgical trials was low for a long time and trials were often linked with limited methodologic quality [5–7]. As a consequence, many surgical procedures have been adopted without high-quality evidence from randomized controlled trials. Justifications for widespread adoption of these procedures are numerous, ranging from an expected huge or exaggerated effectiveness and thus, a resulting lack of equipoise between procedures, inability to standardize surgical procedures, lack of funding by equivalents of the pharmaceutical industry, or ethical concerns to randomize surgical patients. Various entities such as the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) collaboration made substantial efforts to improve quantity and quality of surgical research [8]. In addition, national initiatives such as the Dutch Pancreatic Cancer Group [9] or the Study Center of the German Surgical Society have established an infrastructure for multicenter surgical trials [10]. These collaborative projects have resulted in substantial progress, although there is still room for improvement [11].

The above-mentioned limitations of the surgical evidence-base pertain in particular to complex clinical areas such as pancreatic cancer surgery. However, since surgery is still the mainstay of curative pancreatic cancer therapy, a sufficient amount of well-conducted trials focusing on surgical techniques and strategies would be highly desirable. The following chapter will provide an overview of quantity and quality of surgical trials in pancreatic cancer and their evolution over time.

7.2 Quantity of Surgical Trials in Pancreatic Cancer

In a systematic review of all randomized controlled trials in pancreatic surgery most trials did not focus on a specific disease, but pancreatic ductal adenocarcinoma was the most frequent indication for surgery in 158 of 246 (64.2%) trials from 1984 to 2018 [12]. Therefore, the evidence of these trials appears applicable to patients with pancreatic cancer to a great extent. This textbook and the current chapter are focused on pancreatic cancer surgery and therefore trials assessing (neo-)adjuvant therapy are not considered, even though several (neo-)adjuvant therapy trials were initiated by surgical trial groups [13, 14].

The first surgical trial that focused explicitly on patients with pancreatic cancer—comparing percutaneous transhepatic placement of a biliary endoprosthesis to bypass surgery—was published in 1986 in the Lancet [15]. Since then, the quantity increased slowly. During a 33-year period from 1986 to 2018 a total of 79 surgical trials focusing on pancreatic or periampullary malignancies were published. Taking a closer look at surgical trials that only addressed pancreatic cancer in particular, the number of published trials is only 24. Of the surgical trials in pancreatic cancer, 14 trials were conducted in Europe (58.3%) [16–29], six in Asia (25%) [30–35], two in Africa (8.3%) [15, 36] and one each in North [37] and South America (4.2% respectively) [38]. The surgical procedure under investigation was pancreatoduodenectomy in 16 trials, pancreatoduodenectomy and other resectional procedures (distal or total pancreatectomy) in two, pancreatoduodenectomy and simple exploration or palliative bypass procedures in one, and only palliative bypass procedures in five (biliary in two, gastric in two and both in one trial). The median sample size of these trials was 54 ranging from 12 to 244. Duration of follow-up was not stated in detail in 13 trials and ranged from 2 weeks to 84 months in the remaining 11 trials.

The topic areas of these trials are summarized in Fig. 7.1. The results of most of these trials are discussed in the respective chapters of this textbook.

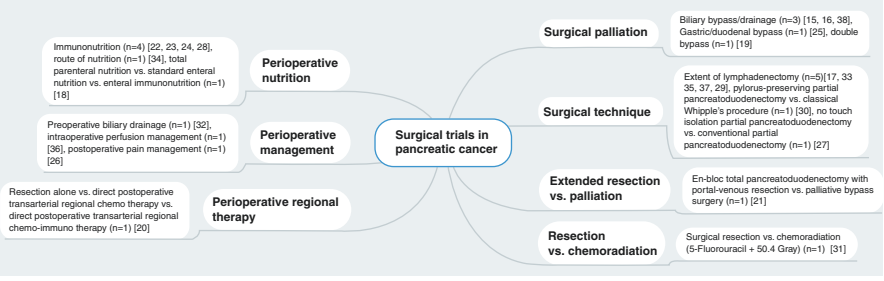

Fig. 7.1 Thematic overview of surgical trials in pancreatic cancer. n = number of trials for respective topic

7.3 Quality of Surgical Trials in Pancreatic Cancer

The overall quality of surgical trials on both, pancreatic cancer and any pancreatic malignancy, was rather low (Fig. 7.2). Especially the domains of blinding leave room for improvement. Furthermore, only a vanishingly low proportion of trials presented a sufficiently detailed trial registration or published protocol that allowed a judgement of 'low risk' of bias for the domain 'selective reporting'.

Furthermore, a large proportion of trials suffer from other forms of bias, such as lack of a valid sample size calculation or industry bias. In addition, the majority of trials (79.2% [19 of 24] trials on pancreatic cancer) were conducted at a single institution often with a small sample size (<100 patients). While the details of the surgical procedures were described in sufficient detail in most trials, only few trials considered surgical learning curves or surgical quality.

7.4 Evolution over Time

To further assess the evolution of surgical trials in pancreatic cancer, the interval from the first trial in 1986 until 2018 was divided into three periods; P-I (1986–1996), P-II (1997–2007), and P-III (2008–2018).

The total number of published trials focusing on any pancreatic malignancy was 11 with a median of one (0–3) trial per year in P-I, 26 with a median of two (0–5) trials per year in P-II, and 40 with a median of four (1–6) trials per year in P-III. This demonstrates a mild trend towards an increase in quantity of surgical trials in this area of research. Looking only at trials on pancreatic cancer, this trend fades with a total of two with a median of zero (0–1) trials per year in P-I, 11 with a median of one (0–2) in P-II, and 11 with a median of one (0–3) in P-III (Fig. 7.3).

Due to the low number of trials focusing particularly on pancreatic cancer, the evolution of quality was assessed in all trials assessing pancreatic malignancies. The quality of surgical trials in pancreatic malignancy appeared to improve over time in nearly all domains of the Cochrane Risk of Bias Tool. However, problematic domains such as 'blinding of participants and personnel' and 'selective reporting' and their reporting are still at low risk of bias in only one quarter of randomized controlled trials (Fig. 7.4).

7.5 The Way Forward

Although pancreatic cancer is the most common indication for pancreatic surgery, the quantity and quality of surgical trials that focus explicitly on pancreatic cancer are limited. Endeavors of various entities led to an increase of quantity in recent years, but these efforts still need further endorsement to overcome existing evidence

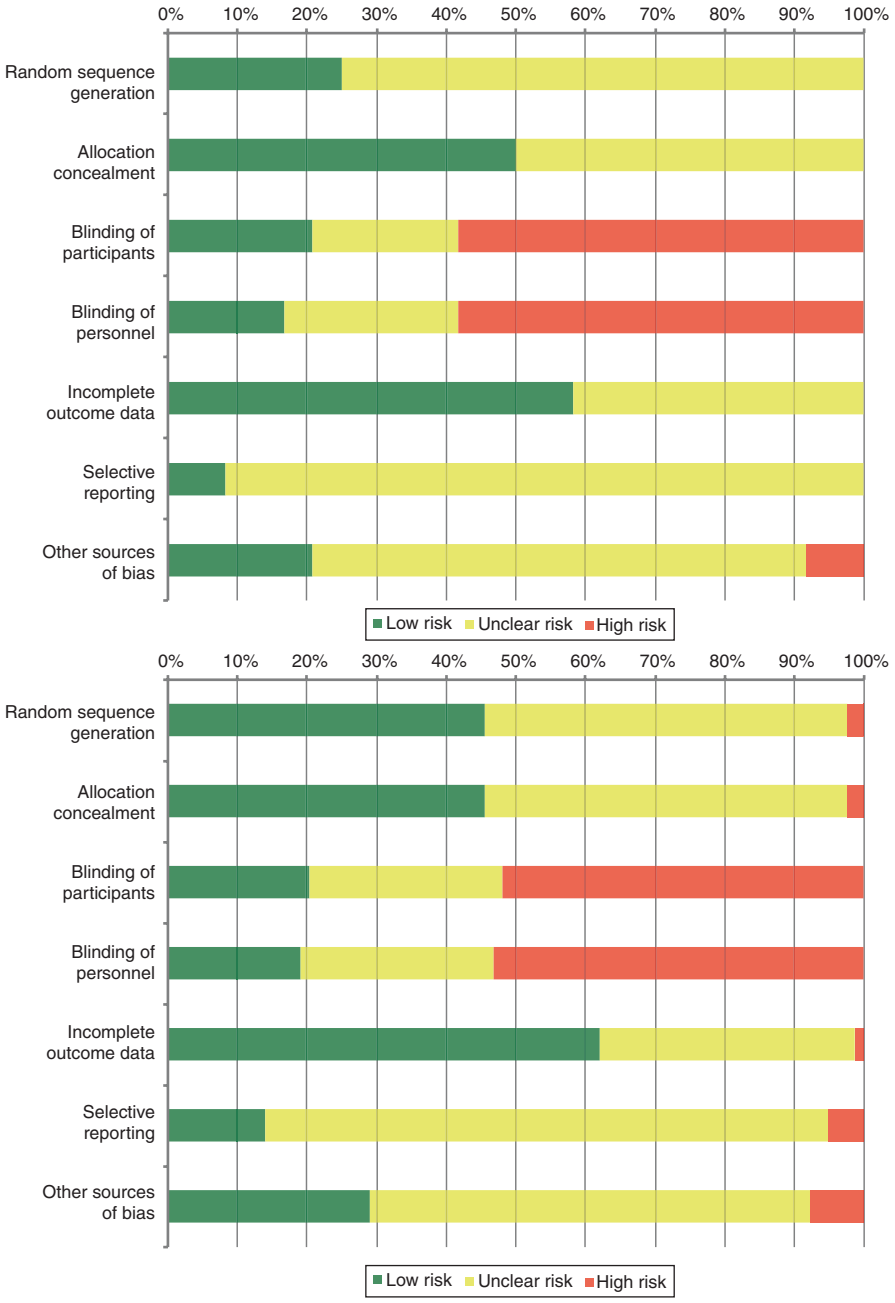

Fig. 7.2 Risk of bias summary. Risk of bias summary of trials on (**a**) pancreatic cancer and (**b**) any pancreatic malignancy

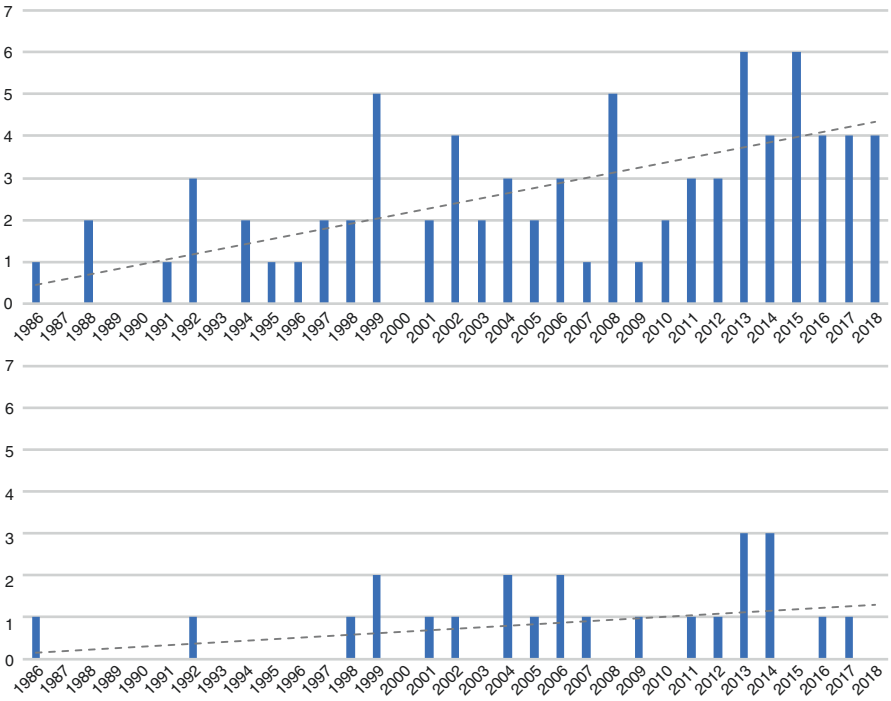

Fig. 7.3 Time trend of annual trial quantity. Number of trials per year for (**a**) any pancreatic malignancy and (**b**) pancreatic cancer

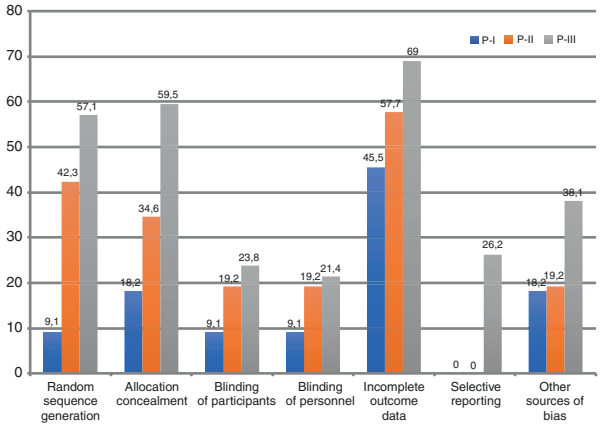

Fig. 7.4 Time trend of trial quality. Proportion of trials at low risk of bias for the three time periods: P-I (1986–1996), P-II (1997–2007), and P-III (2008–2018)

gaps. Despite an increase in quantity, encouragingly it seems that also the quality of conduct and reporting of surgical trials has been increased. However, regarding individual domains for risk of bias such as blinding and selective reporting, there are still substantial shortcomings in trial methodology and reporting.

In accordance with the findings in pancreatic cancer, it has been demonstrated that the quantity of randomized controlled trials in pancreatic surgery in general [12] has increased. Regarding the whole body of surgical research, the proportion of randomized controlled trials in surgical research has increased [39]. Similarly, the quality of randomized controlled trials in different surgical areas has been improved in recent years [40, 41]. On the other hand, it has been shown recently that there is still a considerable amount of waste in surgical randomized controlled trials [42].

In order to 'increase value and reduce waste' in clinical surgical research [43], endeavors by different institutions and entities should be bundled and future research should be prioritized focusing on specific evidence gaps. To achieve these goals, several aspects should be considered:

7.5.1 Research Prioritization

To answer the right questions at the right time, different stakeholders (surgeons, patients, research funders, policy makers, etc.) should make joint decisions on research prioritization. For the purpose of prioritization, novel methods such as priority setting partnerships [44] and evidence mapping [45] can help to focus on the most important issues and to save resources.

Priority setting partnerships involving various stakeholders in a specific field of research can help to address those research questions preferentially that are most relevant to end-users. This concept has recently been applied to pancreatic cancer and results are eagerly awaited.

In addition, the newly created evidence map of pancreatic surgery (www.evidencemap.surgery) addresses the need for condensation and clear visualization of the existing evidence and remaining gaps in the evidence base. To give an example regarding pancreatic cancer surgery: while there are five trials assessing the right extent of resection in pancreatoduodenectomy [17, 29, 33, 35, 37], there is none addressing the right extent of lymphadenectomy in distal pancreatectomy. Specific techniques of distal pancreatectomy for pancreatic cancer such as the radical antegrade modular pancreatosplenectomy are not the intervention under investigation of any surgical trial, although it is frequently applied in clinical practice and even recommended by some guidelines [46].

7.5.2 Collaborative, Pragmatic Surgical Trials

It has been demonstrated several times in surgical research that promising results of small single center trials cannot be corroborated in the rigorous multicenter randomized setting [47, 48]. Therefore, instead of conducting a fairly large number of small single center trials, confirmatory, pragmatic trials with sufficiently large

sample sizes, could and should be conducted by pooling (inter-)national resources and creating collaborations. In a recent analysis, it has been shown that both, external funding and trials conducted in a multicenter setting, are less likely to result in research waste [42]. However, the infrastructure of such collaborative surgical trial groups is scarce in various regions worldwide [49]. National initiatives such as the Dutch Pancreatic Cancer Group [9] or the Study Center of the German Surgical Society [10] have demonstrated that it is possible and worthwhile to establish a multicenter infrastructure for surgical trials. However, international collaborative structures could further improve their efficiency. Furthermore, the increasing costs for randomized controlled trials [50] and the resulting trend towards less trials per amount of governmental funding is alarming [51]. Especially in the United States of America, it seems that this evolution has even resulted in a reversed trend of quantity of surgical trials in recent years [40]. An established infrastructure of collaborative surgical trial groups can help to limit expenses for surgical trials by an increased efficiency in trial conduct.

7.5.3 Focus on Methodology and Training Programs

With the intention of increasing quality of surgical trials, the awareness for the methodological basis of good clinical research should be raised within training programs for surgical researchers. Additionally, the recommendations conceived in the IDEAL framework should be followed to warrant a certain degree of quality [8]. Regarding specific shortcomings in the present surgical trials in pancreatic cancer 'blinding' is the domain that is least often at low risk of bias. While it is clear that a trial comparing surgical to endoscopic palliation of biliary obstruction cannot be reasonably blinded, a large proportion of the present trials could have been blinded at least for some of the trial contributors. The classical 'double-blind' trial design is not sufficient for surgical trials and therefore reports should be more specific to which trial contributors have actually been blinded [52]. The second most limited quality domain in pancreatic cancer surgery trials is 'selective reporting'. Selective reporting has been identified as a frequent problem in surgical trials before [53]. In this regard, there are no specific challenges in surgical trials that could explain or excuse this shortcoming. Trial protocols should be published or made publicly available and if this is not possible or intended, the trial registration, which is mandatory to comply with the Declaration of Helsinki, should contain sufficient information on all endpoints of a specific trial.

7.5.4 Transfer of Knowledge to Clinical Practice

Finally, transfer of knowledge from surgical trials into clinical practice remains challenging. The most striking issue in this regard is that still more than one quarter of surgical randomized controlled trials remain unpublished [42]. Additionally, the

adoption from results of surgical trials into surgical practice is at best moderate [54]. Although, the underlying reasons are unclear, this finding raises concerns regarding knowledge transfer of surgical trials. In the contemporary fast-paced scientific society, the classical way of solely publishing results of surgical research in a scientific journal may not be timely anymore. To transport the results of surgical research to end-users (patients as well as medical professionals) all possible channels of knowledge transfer, including web-based information, social media, information sessions for various audiences etc., need to be considered in addition to a peer-reviewed scientific publication. For this purpose, the process of knowledge transfer needs professionalization from surgical researchers or even dedicated knowledge transfer experts.

7.6 Conclusions

Prospective randomized controlled trials are still the only clinical research method that can provide direct proofs of causality. Thus, randomized controlled trials will remain the main pillar of evidence-based medicine and surgery. During the last 30 years the evidence base of surgical trials in pancreatic cancer has steadily increased. But, the above-mentioned issues and the current increasing interest of medical and surgical scientists in big data analyses and similar methods could even lead to a regression in quantity of surgical trials. This evolution needs to be counteracted to preserve evidence-based recommendations for the individual problems of patients in the future including but not limited to pancreatic cancer. Despite the above-mentioned recommendations, this could be achieved by specific incentives promoting randomized controlled surgical trials by funding organizations and surgical journals.

References

1. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, et al. Challenges in evaluating surgical innovation. Lancet. 2009;374(9695):1097–104. https://doi.org/10.1016/S0140-6736(09)61086-2.
2. Hüttner FJ, Doerr-Harim C, Probst P, Tenckhoff S, Knebel P, Diener MK. Study methods in evidence-based surgery: methodological impediments and suggested approaches for the creation and transfer of knowledge in surgery. Eur Surg Res. 2014;53(1–4):86–94. https://doi.org/10.1159/000366201.
3. Doerr-Harim C, Bruckner T, Diener MK, Knebel P. Insights into surgical trials: methodological challenges and solutions. Langenbeck's Arch Surg. 2014;399(3):273–8. https://doi.org/10.1007/s00423-013-1155-5.
4. Probst P, Grummich K, Harnoss JC, Hüttner FJ, Jensen K, Braun S, et al. Placebo-controlled trials in surgery: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(17):e3516. https://doi.org/10.1097/MD.0000000000003516.
5. Shawhan RR, Hatch QM, Bingham JR, Nelson DW, Fitzpatrick EB, McLeod R, et al. Have we progressed in the surgical literature? Thirty-year trends in clinical studies in 3 surgical journals. Dis Colon Rectum. 2015;58(1):115–21. https://doi.org/10.1097/DCR.0000000000000273.

6. Solomon MJ, Laxamana A, Devore L, McLeod RS. Randomized controlled trials in surgery. Surgery. 1994;115(6):707–12.
7. Wente MN, Seiler CM, Uhl W, Buchler MW. Perspectives of evidence-based surgery. Dig Surg. 2003;20(4):263–9. https://doi.org/10.1159/000071183.
8. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105–12. https://doi.org/10.1016/S0140-6736(09)61116-8.
9. Dutch Pancreatic Cancer Group. http://www.dpcg.nl. Accessed 26 Oct 2019.
10. Probst P, Klaiber U, Hüttner F, Doerr-Harim C, Knebel P, Rossion I et al. [Evidence-based surgery—the Study Center of the German Surgical Society]. Z Evid Fortbild Qual Gesundhwes. 2015;109(3):199–210. doi:https://doi.org/10.1016/j.zefq.2015.03.001.
11. McCulloch P, Feinberg J, Philippou Y, Kolias A, Kehoe S, Lancaster G, et al. Progress in clinical research in surgery and IDEAL. Lancet. 2018;392(10141):88–94. https://doi.org/10.1016/S0140-6736(18)30102-8.
12. Hüttner FJ, Capdeville L, Pianka F, Ulrich A, Hackert T, Büchler MW, et al. Systematic review of the quantity and quality of randomized clinical trials in pancreatic surgery. Br J Surg. 2019;106(1):23–31. https://doi.org/10.1002/bjs.11030.
13. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA. 2012;308(2):147–56. https://doi.org/10.1001/jama.2012.7352.
14. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24. https://doi.org/10.1016/S0140-6736(16)32409-6.
15. Bornman PC, Harries-Jones EP, Tobias R, Van Stiegmann G, Terblanche J. Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas. Lancet. 1986;1(8472):69–71. https://doi.org/10.1016/s0140-6736(86)90719-1.
16. Gullichsen R, Havia T, Ovaska J, Rantala A. Cholecystoenteral anastomosis with the biofragmentable ring and manual suture—a prospective, randomized study. Ann Chir Gynaecol. 1992;81(4):354–6.
17. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg. 1998;228(4):508–17. https://doi.org/10.1097/00000658-199810000-00007.
18. Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. Complications of pancreatic surgery and the role of perioperative nutrition. Dig Surg. 1999;16(4):320–6. https://doi.org/10.1159/000018742.
19. Yilmaz S, Kirimlioglu V, Katz DA, Kayaalp C, Caglikulekci M, Ara C. Randomised clinical trial of two bypass operations for unresectable cancer of the pancreatic head. Eur J Surg. 2001;167(10):770–6. https://doi.org/10.1080/11024150152707761.
20. Lygidakis NJ, Sgourakis G, Georgia D, Vlachos L, Raptis S. Regional targeting chemoimmunotherapy in patients undergoing pancreatic resection in an advanced stage of their disease: a prospective randomized study. Ann Surg. 2002;236(6):806–13. https://doi.org/10.1097/00000658-200212000-00013.
21. Lygidakis NJ, Singh G, Bardaxoglou E, Dedemadi G, Sgourakis G, Nestoridis J, et al. Monobloc total spleno-pancreaticoduodenectomy for pancreatic head carcinoma with portal-mesenteric venous invasion. A prospective randomized study. Hepato-Gastroenterology. 2004;51(56):427–33.
22. Slotwinski R, Olszewski WL, Slotkowski M, Lech G, Zaleska M, Slotwinska SM, et al. Can the interleukin-1 receptor antagonist (IL-1ra) be a marker of anti-inflammatory response

to enteral immunonutrition in malnourished patients after pancreaticoduodenectomy? JOP. 2007;8(6):759–69.
23. Uggeri F, Caprotti R, De Grate L, Crippa S, Nobili C, Penati C, et al. Short-term preoperative IL-2 immunotherapy in operable pancreatic cancer: a randomized study. Hepato-Gastroenterology. 2009;56(91–92):861–5.
24. Slotwinski R, Olszewski W, Slodkowski M, Lech G, Zaleska M, Kedziora S, et al. Apoptosis in lymphocytes of pancreatic cancer patients: influence of preoperative enteral immunonutrition and extensive surgery. Arch Immunol Ther Exp. 2011;59(5):385–97. https://doi.org/10.1007/s00005-011-0140-3.
25. Szymanski D, Durczynski A, Nowicki M, Strzelczyk J. Gastrojejunostomy in patients with unresectable pancreatic head cancer—the use of Roux loop significantly shortens the hospital length of stay. World J Gastroenterol. 2013;19(45):8321–5. https://doi.org/10.3748/wjg.v19.i45.8321.
26. Bjersa K, Andersson T. High frequency TENS as a complement for pain relief in postoperative transition from epidural to general analgesia after pancreatic resection. Complement Ther Clin Pract. 2014;20(1):5–10. https://doi.org/10.1016/j.ctcp.2013.11.004.
27. Gall TM, Jacob J, Frampton AE, Krell J, Kyriakides C, Castellano L, et al. Reduced dissemination of circulating tumor cells with no-touch isolation surgical technique in patients with pancreatic cancer. JAMA Surg. 2014;149(5):482–5. https://doi.org/10.1001/jamasurg.2013.3643.
28. Gade J, Levring T, Hillingso J, Hansen CP, Andersen JR. The effect of preoperative oral immunonutrition on complications and length of hospital stay after elective surgery for pancreatic cancer—a randomized controlled trial. Nutr Cancer. 2016;68(2):225–33. https://doi.org/10.1080/01635581.2016.1142586.
29. Ignjatovic I, Knezevic S, Knezevic D, Dugalic V, Micev M, Matic S, et al. Standard versus extended lymphadenectomy in radical surgical treatment for pancreatic head carcinoma. J BUON. 2017;22(1):232–8.
30. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg. 1999;86(5):603–7. https://doi.org/10.1046/j.1365-2168.1999.01074.x.
31. Imamura M, Doi R, Imaizumi T, Funakoshi A, Wakasugi H, Sunamura M, et al. A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer. Surgery. 2004;136(5):1003–11. https://doi.org/10.1016/j.surg.2004.04.030.
32. Tian FZ, Shi L, Tang LJ, Wang T, Li DX, Zou S, et al. [Perspective of pre-operational jaundice-reducing indication in carcinoma of head of pancreas]. Zhonghua Wai Ke Za Zhi. 2006;44(23):1614–6.
33. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012;19(3):230–41. https://doi.org/10.1007/s00534-011-0466-6.
34. Guo JC, Li J, Hu Y, Zhang TP, Liao Q, Dai MH, et al. [The role of perioperative enteral and parenteral nutrition treatment in pancreatic cancer: a multicenter, prospective randomized controlled trial]. Zhonghua Wai Ke Za Zhi. 2013;51(11):987–90.
35. Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg. 2014;259(4):656–64. https://doi.org/10.1097/SLA.0000000000000384.
36. Reyad AR, Elkharboutly W, Wahba A, Elmorshedi M, Hasaneen NA. Effect of intraoperative dobutamine on splanchnic tissue perfusion and outcome after Whipple surgery. J Crit Care. 2013;28(4):531.e7–15. https://doi.org/10.1016/j.jcrc.2013.02.017.
37. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–28.; ; discussion 28–30. https://doi.org/10.1016/j.surg.2005.06.044.

38. Artifon EL, Sakai P, Cunha JE, Dupont A, Filho FM, Hondo FY, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. Am J Gastroenterol. 2006;101(9):2031–7. https://doi.org/10.1111/j.1572-0241.2006.00764.x.
39. Brooke BS, Nathan H, Pawlik TM. Trends in the quality of highly cited surgical research over the past 20 years. Ann Surg. 2009;249(1):162–7. https://doi.org/10.1097/SLA.0b013e3181929 1f9.
40. Ahmed Ali U, van der Sluis PC, Issa Y, Habaga IA, Gooszen HG, Flum DR, et al. Trends in worldwide volume and methodological quality of surgical randomized controlled trials. Ann Surg. 2013;258(2):199–207. https://doi.org/10.1097/SLA.0b013e31829c7795.
41. Antoniou SA, Andreou A, Antoniou GA, Koch OO, Kohler G, Luketina RR, et al. Volume and methodological quality of randomized controlled trials in laparoscopic surgery: assessment over a 10-year period. Am J Surg. 2015;210(5):922–9. https://doi.org/10.1016/j.amjsurg.2015.04.022.
42. Chapman SJ, Aldaffaa M, Downey CL, Jayne DG. Research waste in surgical randomized controlled trials. Br J Surg. 2019;106(11):1464–71. https://doi.org/10.1002/bjs.11266.
43. Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. Lancet. 2014;383(9912):101–4. https://doi.org/10.1016/S0140-6736(13)62329-6.
44. Staley K, Crowe S. More than a top 10: how James Lind Alliance priority setting partnerships transform research, people and organisations; 2019.
45. Probst P, Hüttner FJ, Meydan O, Kalkum E, Kretschmer R, Jensen K, et al. Evidence map of pancreatic surgery: protocol for a living systematic review and meta-analysis. BMJ Open. 2019;9(9):e032353. https://doi.org/10.1136/bmjopen-2019-032353.
46. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68. https://doi.org/10.1093/annonc/mdv295.
47. Diener MK, Hüttner FJ, Kieser M, Knebel P, Dorr-Harim C, Distler M, et al. Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial. Lancet. 2017;390(10099):1027–37. https://doi.org/10.1016/S0140-6736(17)31960-8.
48. Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet. 2011;377(9776):1514–22. https://doi.org/10.1016/S0140-6736(11)60237-7.
49. Reynolds T. Why randomized surgical oncology trials are so scarce. J Natl Cancer Inst. 1999;91(14):1182–3. https://doi.org/10.1093/jnci/91.14.1182.
50. Shore BJ, Nasreddine AY, Kocher MS. Overcoming the funding challenge: the cost of randomized controlled trials in the next decade. J Bone Joint Surg Am. 2012;94(Suppl 1):101–6. https://doi.org/10.2106/JBJS.L.00193.
51. Forrester JA, Forrester JD, Wren SM. Trends in country-specific surgical randomized clinical trial publications. JAMA Surg. 2018;153(4):386–8. https://doi.org/10.1001/jamasurg.2017.4867.
52. Probst P, Zaschke S, Heger P, Harnoss JC, Hüttner FJ, Mihaljevic AL, et al. Evidence-based recommendations for blinding in surgical trials. Langenbeck's Arch Surg. 2019;404(3):273–84. https://doi.org/10.1007/s00423-019-01761-6.
53. Rosenthal R, Dwan K. Comparison of randomized controlled trial registry entries and content of reports in surgery journals. Ann Surg. 2013;257(6):1007–15. https://doi.org/10.1097/SLA.0b013e318283cf7f.
54. Oberkofler CE, Hamming JF, Staiger RD, Brosi P, Biondo S, Farges O, et al. Procedural surgical RCTs in daily practice: do surgeons adopt or is it just a waste of time? Ann Surg. 2019;270(5):727–34. https://doi.org/10.1097/SLA.0000000000003546.

Chapter 8
Mandatory Reporting Measurements in Trials for Potentially Resectable Pancreatic Cancer

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Take Home Messages
- 14 baseline and 7 prognostic characteristics for potentially resectable pancreatic cancer trials are mandatory to be included in future clinical trials.
- Mandatory reporting of factors should allow for better outcome comparisons of future studies and facilitates new studies in the field of potentially resectable pancreatic cancer.

Pearls and Pitfalls

Pearls
- Definition of prognostic factors is of major importance to generate conclusions and standardization of care in potentially resectable pancreatic cancer patients.
- The baseline and prognostic factors identified in this study are uniformly presented in the different studies based on a large number of randomized patients.
- Clinical relevance of prognostic factors is assessed per criteria of Ter Veer et al. [1].

Pitfalls
- Nowadays, mainly imprecisely defined prognostic factors are described in clinical trials, be critical on the definition.
- Newly identified e.g. molecular-based prognostic factors have not (yet) been analyzed in RCTs and are therefore not included in this chapter.
- Failure of reporting of factors in previous research might have led to an erroneous exclusion of some factors due to lack of reporting.

Future Perspectives
- Validation of the prognostic factors that were found to be clinically relevant in large cohort studies.

8.1 Introduction

Treatment decisions for patients with potentially resectable pancreatic cancer have become increasingly complex. (Neo)adjuvant therapy has been proposed in addition to surgery alone, but, unfortunately, around 50% of patients fail to receive adjuvant therapy due to post-operative complications, patient preference or disease progression [2]. Therefore, the benefits of different treatment trajectories, including high risk surgery with major impact on quality of life, high morbidity and mortality and poor survival outcomes, have to be properly considered with the patient in a process

Box 8.1 Definition of Prognostic and Predictive Factors
A *prognostic* factor is a measurement related to the clinical outcome without the use of therapy or with standard therapy only. The control group in a randomized controlled trial can be used to determine the prognostic value of a biomarker [5].

A *predictive* factor is a measurement related to response or absence of response to a therapy. It describes the relationship between predictive factor and the treatment benefit and makes it possible to select the therapy with the highest likelihood of efficacy to the individual patient [5, 6].

of shared decision making [3]. Adequate information on outcomes is crucial in this process and prognostic and predictive measures may help in decision making for individual patients [2].

"Prognostic" and "predictive" are terms that describe the clinical relationship between a specific factor, for example performance status, and a certain outcome, for example survival. Unfortunately these terms are rarely well-used and often seen as identical terminologies in many publications [4]. In this chapter, we use the definitions as suggested by Clark et al. 2006. A *prognostic* factor is a measurement related to the clinical outcome without the use of therapy or with standard therapy only. The control group in a randomized controlled trial can be used to determine the prognostic value of a biomarker [5]. A *predictive* factor is a measurement related to response or absence of response to a therapy. It describes the relationship between predictive factor and the treatment benefit and makes it possible to select the therapy with the highest likelihood of efficacy to the individual patient (e.g. KRAS mutational status is a predictive factor for anti-EGFR (cetuximab) treatment, as downstream mutation in KRAS would predict failure of EGFR pathway inhibition in colorectal cancer) (see Box 8.1) [5, 6]. The response can be measured with any of the commonly used outcomes in clinical trials [4, 5].

In the hierarchy of evidence, systematic reviews with meta-analysis could provide the most robust and reliable evidence [7, 8]. To allow for comparisons between clinical trials and perform meta-analyses, a uniform description of the study population (i.e. the reporting of baseline characteristics) is necessary. With baseline characteristics the study population is defined at the start of the trial, these characteristics do not necessarily have a relation with the outcome of the trial (e.g. survival). In contrast, prognostic factors do have a relationship with the outcome of a trial (e.g. survival). By standardization of reporting of these baseline and prognostic characteristics, possible confounders can be identified and allow for a better comparison of outcomes across studies. For patients with unresectable disease, a consensus statement from a group of experts in the field of pancreatic cancer is available on mandatory and recommended measurements of baseline and prognostic characteristics to be included in trials for this patient population [9]. This includes a list of 23 mandatory baseline characteristics (e.g., age, sex, tumor differentiation) and 12 mandatory prognostic characteristics (e.g. CA 19-9, liver metastasis, performance status) to be included in future randomized controlled trials [9].

Despite the fact that the interest in predictive and prognostic factors in pancreatic cancer is growing, the availability of prognostic research and methodologies is limited in the surgical literature for pancreatic cancer [10, 11]. In this chapter we aim to describe baseline and prognostic characteristics, which are regarded mandatory in trials for patients with potentially resectable pancreatic ductal adenocarcinoma (PDAC) based on the currently available literature.

8.2 Baseline Characteristics in Trials of Patients with Potentially Resectable Pancreatic Cancer

Given the current knowledge gap on relevant baseline and prognostic variables for patients with potentially resectable pancreatic cancer, we performed a systematic review following the PRISMA guidelines and searched the electronic databases PubMed, Embase and the Cochraine Register Controlled Trials (CENTRAL) for randomized controlled trials investigating surgery as a treatment for potentially resectable pancreatic cancer patients with or without (neo)adjuvant therapy. Eligibility criteria for inclusion were English language, published after January 2000, randomized controlled trial, patients aged 18 years or older, histopathologically proven PDAC in at least 70% of the study population, potentially resectable pancreatic cancer with or without (neo)adjuvant therapy, and overall survival as an endpoint. A total of 2883 titles were retrieved from our database search. After title and abstract screening 79 studies remained for full text assessment, resulting in 39 studies that were eligible and contained information on 8993 patients (see Fig. 8.1) [12–41].

Baseline characteristics were extracted from the 39 included studies in order to create a structured overview of all reported baseline characteristics. Mandatory baseline characteristics were selected based upon the most frequently reported

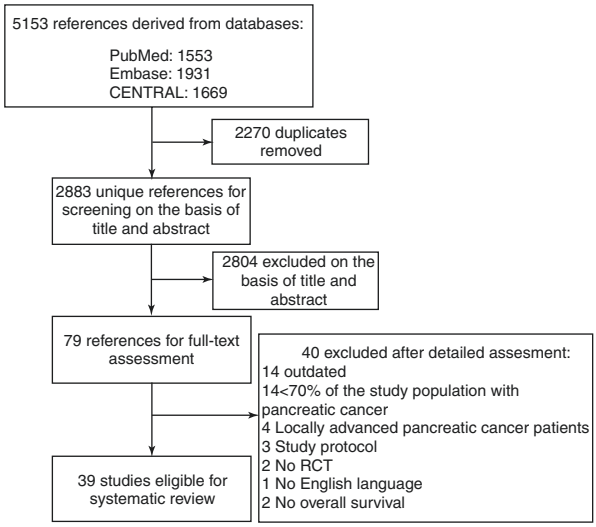

Fig. 8.1 Literature search. Flowchart of our literature search used in the identification of baseline and prognostic factors for potential pancreatic cancer patients. *CENTRAL* Cochrane Central Register of Controlled Trials, *RCT* randomized controlled trial

characteristics. A characteristic was defined as such when the number of studies describing that characteristics were more than 45% of the total number of studies. For example, when the characteristic 'age' was studied in 30 of the 40 studies, 'age' would be defined as a frequently reported factor because it was included in 75% of the total number of RCTs.

We identified a total of 61 baseline characteristics and the most frequently reported were: age (n = 38 studies), sex (n = 37), surgical resection margins (n = 25), pT stage (n = 20), tumor size (n = 19), pN stage (n = 18) and performance status (n = 18) (see Fig. 8.2). Also, for trials on patients with unresectable PDAC age, sex and performance status were identified as frequently reported baseline characteristics [9]. To allow for cross trial comparisons between studies on patients with potential resectable and unresectable PDAC, we advocate that at least age, sex and performance status are reported as mandatory baseline characteristics.

8.3 Prognostic Factors in Trials of Patients with Potentially Resectable Pancreatic Cancer

To identify potential prognostic factors for overall survival we adopted the criteria as previously described by Ter Veer et al. to determine the clinical relevance of the prognostic factors: to reach clinical relevance a prognostic factor should be statistically significant in a multivariate regression analysis ($p \leq 0.05$) in at least one RCT, the combined sample size of all RCTs in which that specific factor was statistically significant should be >50% of the total sample size of all RCTs reporting that factor [1]. For example, if three RCTs report the factor 'sex' (total 1000 patients) and in two (300 patients) of the three studies the factor is statistically significant, this factor is not clinically relevant since 300 of 1000 is 30%, which does not exceed the required limit of 50%.

Prognostic factors were regarded mandatory when the factor was studied in at least three trials and were found to be clinically relevant based upon the criteria mentioned above.

Seventeen studies (44%) reported a multivariate regression analysis with overall survival as an endpoint. In total, 20 unique prognostic factors were identified from which 11 were found to be clinically relevant: patient characteristics; performance status, smoking status, age, tumor characteristics; nodal status, tumor size, postoperative CA 19-9, tumor grade, tumor stage, endovascular tumor emboli, treatment characteristics; adjuvant therapy and portal vein resection. The most frequently studied prognostic factors were adjuvant therapy (n = 10), nodal status (n = 9), tumor grade (n = 8), tumor size (n = 8) and surgical margin status (n = 7), the latter one not being statistically significant in the majority of studies (see Fig. 8.3, Boxes 8.2 and 8.3). These frequently reported prognostic factors showed no overlap with the factors found to be the five most frequently reported in trials for unresectable pancreatic cancer patients. Indeed, in patients with potentially resectable pancreatic cancer other prognostic factors (e.g. surgical margins, tumor size) are important compared to unresectable patients (disease status; locally advanced pancreatic cancer vs metastatic pancreatic cancer).

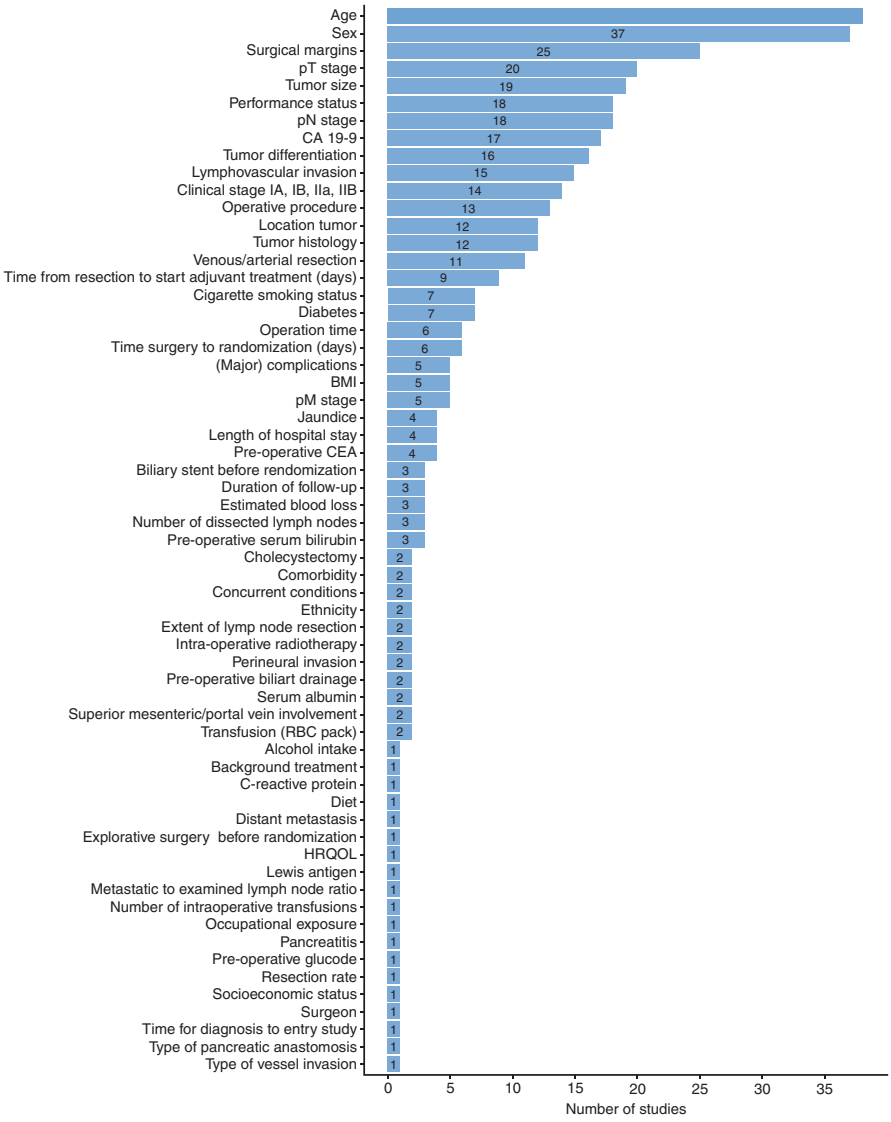

Fig. 8.2 Baseline characteristics. The y-axis shows the identified baseline characteristics and the x-axis shows the number of randomized controlled trials in which the characteristic was reported. *CA 19-9* cancer antigen (CA) 19–9, *BMI* body mass index, *CEA* carcinoembryonic antigen, *RBC pack* red blood cell pack, *HRQOL* health related quality of life

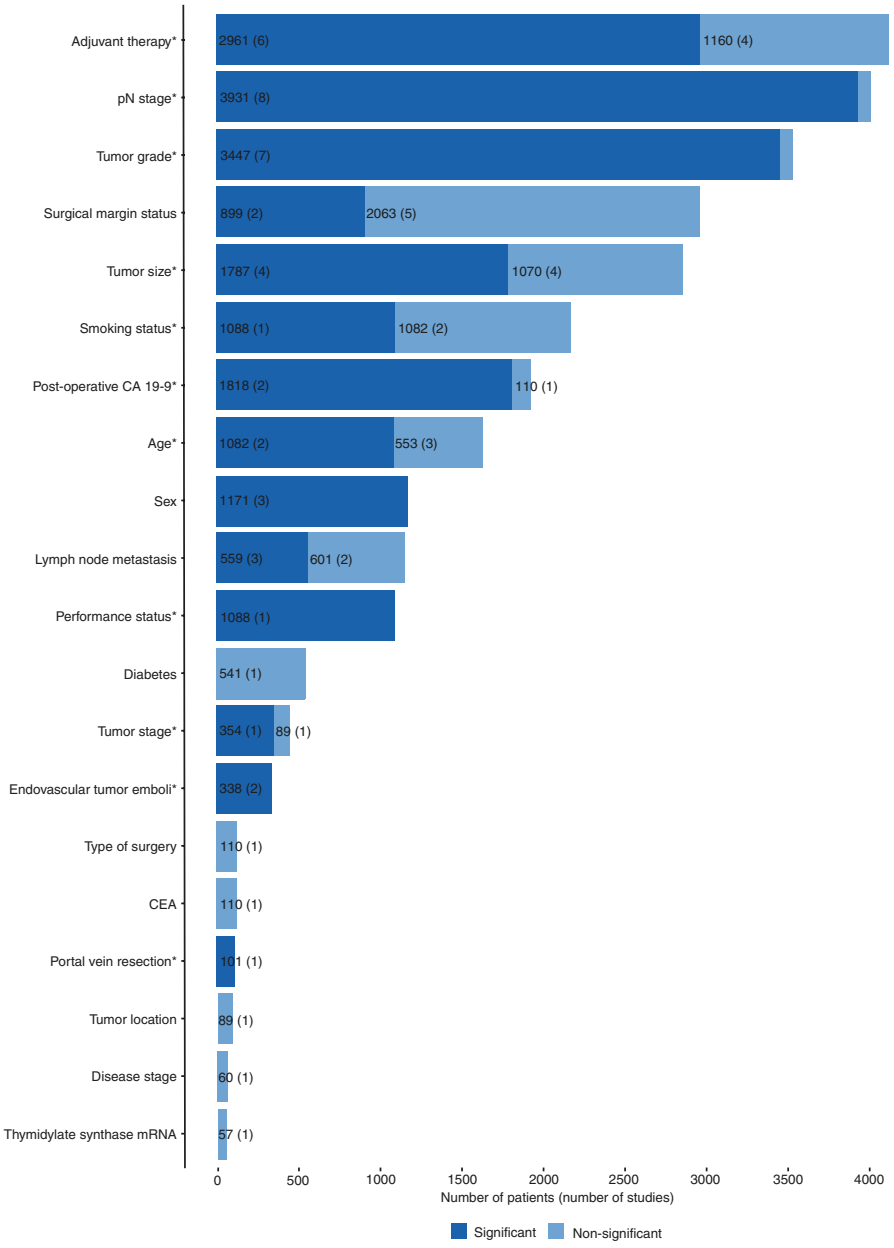

Fig. 8.3 Prognostic factors for overall survival. All factors have been included in a multivariate regression analysis in at least one RCT. *The factors that met the criteria for clinical relevance. *CA 19-9* cancer antigen (CA) 19–9, *CEA* carcinoembryonic antigen, *mRNA* messenger ribonucleic acid

Box 8.2 Mandatory Baseline Characteristics in Randomized Controlled Trials for Potentially Resectable Pancreatic Cancer

- Age
- Sex
- Surgical margins
- T stage
- Tumor size
- N stage
- Performance status
- CA 19-9
- Tumor differentiation
- Lymphovascular invasion
- Clinical stage
- Operative procedure
- Location tumor
- Tumor histology

Box 8.3 Mandatory Prognostic Factors in Randomized Controlled Trials for Potentially Resectable Pancreatic Cancer

- Adjuvant therapy
- Nodal status
- Tumor grade
- Tumor size
- Smoking status
- Post-operative CA 19-9
- Age

Future Perspectives

In future clinical trials, the clinically relevant factors that we identified can be pre-specified, used as stratification factor and accounted for as possible predictors in regression analyses. Future research should validate the clinically relevant prognostic factors found in this study using large cohort studies to allow for the establishment of a comprehensive prognostic index [1].

Interestingly, based on the currently available randomized trials only one biomarker—thymidylate synthase mRNA—was included as a prognostic marker. A biomarkers is defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or

intervention [42]. Lately, molecular and genetic characteristics have been identified as important factors determining survival of pancreatic cancer [43, 44]. RNA expression analysis has been performed in several studies defining different epithelial and stromal PDAC subtypes. Bailey et al. (2016) described 4 epithelial subtypes: squamous (TP53 and KDM6A mutations), pancreatic progenitor (FOXA2/3, PDX1 and MNX1), immunogenic (pathways involved in acquired immune suppression) and aberrantly differentiated endocrine exocrine (ADEX, KRAS activation NR5A2, RBPJL, NEUROD1 and NKX2-2) that correlate with histopathological characteristics [43]. In the classification by Collison et al. (2019) three epithelial subtypes were identified; squamous, immunogenic progenitor and ADEX [44]. Although the Bailey and Collison subtypes do show overlap, they are not identical. In yet another study only two epithelial subtypes were defined: classical/progenitor vs. basal-like/squamous [45]. The exocrine subtypes might be confounded by contaminated acinar tissue and are therefore not mentioned in this study [45]. The COMPASS trial confirmed the RNA-signature of these two subtypes and was able to show prospectively that patients with the basal subtype typically do not respond to standard chemotherapy [46]. Stromal subtypes have also been distinguished and are not directly associated with epithelial subtypes, these include Normal stroma and Activated stroma [44]. In addition to RNA expression analyses, mutational analysis has shown that BRCA mutations are frequently associated with an inferior prognosis of pancreatic cancer [47–49]. However, BRCA mutated pancreatic cancer is reported to better respond to platinum containing chemotherapeutic regimens compared to sporadic pancreatic cancer, making it both a prognostic and predictive marker [50–52]. Remarkably, none of the RCT's included in our search investigated other biomarkers than thymidylate synthase mRNA as a prognostic factor and were therefore not included in our analysis. Consensus on the most promising biomarkers is urgently needed in order to include these in future randomized controlled trials.

8.4 Conclusion

Meta-analyses of outcomes of clinical trials are essential for standardization of care for pancreatic cancer patients. They allow for better outcome comparisons of future studies and may provide the most appropriate control arm for new studies in the field of potentially resectable pancreatic cancer [9]. We defined mandatory baseline characteristics as the most frequently reported characteristic, when the number of studies describing that characteristics included more than 45% of the complete study sample. Prognostic factors were regarded mandatory if they were studied in at least three trials and were found to be clinically relevant. Based on these criteria and the currently available randomized controlled trials in potentially resectable pancreatic cancer, we advise 14 baseline and 7 prognostic characteristics as mandatory covariates for future clinical trials (see Boxes 8.2 and 8.3). To further advance the field, we also recommend to include novel molecular markers in future trials on resectable pancreatic cancer.

References

1. Ter Veer E, van Kleef JJ, Schokker S, van der Woude SO, Laarman M, Haj Mohammad N, et al. Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: a systematic review and meta-analysis. Eur J Cancer. 2018;103:214–26.
2. Bradley A, Van der Meer R, McKay CJ. A prognostic Bayesian network that makes personalized predictions of poor prognostic outcome post resection of pancreatic ductal adenocarcinoma. PLoS One. 2019;14(9):e0222270.
3. Henselmans I, van Laarhoven HWM, de Haes H, Tokat M, Engelhardt EG, van Maarschalkerweerd PEA, et al. Training for medical oncologists on shared decision-making about palliative chemotherapy: a randomized controlled trial. Oncologist. 2019;24(2):259–65.
4. Clark GM. Prognostic factors versus predictive factors: examples from a clinical trial of erlotinib. Mol Oncol. 2008;1(4):406–12.
5. Clark GM, Zborowski DM, Culbertson JL, Whitehead M, Savoie M, Seymour L, et al. Clinical utility of epidermal growth factor receptor expression for selecting patients with advanced non-small cell lung cancer for treatment with erlotinib. J Thorac Oncol. 2006;1(8):837–46.
6. Le N, Sund M, Vinci A, Pancreas Gcgo. Prognostic and predictive markers in pancreatic adenocarcinoma. Dig Liver Dis. 2016;48(3):223–30.
7. Leucht S, Chaimani A, Cipriani AS, Davis JM, Furukawa TA, Salanti G. Network meta-analyses should be the highest level of evidence in treatment guidelines. Eur Arch Psychiatry Clin Neurosci. 2016;266(6):477–80.
8. Ter Veer E, van Oijen MGH, van Laarhoven HWM. The use of (network) meta-analysis in clinical oncology. Front Oncol. 2019;9:822.
9. Ter Veer E, van Rijssen LB, Besselink MG, Mali RMA, Berlin JD, Boeck S, et al. Consensus statement on mandatory measurements in pancreatic cancer trials (COMM-PACT) for systemic treatment of unresectable disease. Lancet Oncol. 2018;19(3):e151–e60.
10. Bradley A, Van Der Meer R, McKay CJ. A systematic review of methodological quality of model development studies predicting prognostic outcome for resectable pancreatic cancer. BMJ Open. 2019;9(8):e027192.
11. Lewis RS Jr, Vollmer CM Jr. Risk scores and prognostic models in surgery: pancreas resection as a paradigm. Curr Probl Surg. 2012;49(12):731–95.
12. Abrams RA, Winter KA, Regine WF, Safran H, Hoffman JP, Lustig R, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys. 2012;82(2):809–16.
13. Caprotti R, Brivio F, Fumagalli L, Nobili C, Degrate L, Lissoni P, et al. Free-from-progression period and overall short preoperative immunotherapy with IL-2 increases the survival of pancreatic cancer patients treated with macroscopically radical surgery. Anticancer Res. 2008;28(3):1951–4.
14. Casadei R, Di Marco M, Ricci C, Santini D, Serra C, Calculli L, et al. Neoadjuvant chemoradiotherapy and surgery versus surgery alone in resectable pancreatic cancer: a single-center prospective, randomized, controlled trial which failed to achieve accrual targets. J Gastrointest Surg. 2015;19(10):1802–12.
15. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
16. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–28; discussion 28–30.
17. Gall TM, Jacob J, Frampton AE, Krell J, Kyriakides C, Castellano L, et al. Reduced dissemination of circulating tumor cells with no-touch isolation surgical technique in patients with pancreatic cancer. JAMA Surg. 2014;149(5):482–5.
18. Golcher H, Brunner TB, Witzigmann H, Marti L, Bechstein WO, Bruns C, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery

in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015;191(1):7–16.
19. Hagiwara Y, Ohashi Y, Uesaka K, Boku N, Fukutomi A, Okamura Y, et al. Health-related quality of life of adjuvant chemotherapy with S-1 versus gemcitabine for resected pancreatic cancer: results from a randomised phase III trial (JASPAC 01). Eur J Cancer. 2018;93:79–88.
20. Ignjatovic I, Knezevic S, Knezevic D, Dugalic V, Micev M, Matic S, et al. Standard versus extended lymphadenectomy in radical surgical treatment for pancreatic head carcinoma. J BUON. 2017;22(1):232–8.
21. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268(2):215–22.
22. Jang JY, Kang JS, Han Y, Heo JS, Choi SH, Choi DW, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for pancreatic head cancer: a multicenter prospective randomized controlled study. J Hepatobiliary Pancreat Sci. 2017;24(7):426–33.
23. Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg. 2014;259(4):656–64.
24. Lygidakis NJ, Sgourakis G, Georgia D, Vlachos L, Raptis S. Regional targeting chemoimmunotherapy in patients undergoing pancreatic resection in an advanced stage of their disease: a prospective randomized study. Ann Surg. 2002;236(6):806–13.
25. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
26. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
27. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012;19(3):230–41.
28. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
29. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
30. Pal S, Mangla V, Kilambi R, George J, Dash NR, Chattopadhyay TK, et al. An intergroup randomized phase II study of bevacizumab or cetuximab in combination with gemcitabine and in combination with chemoradiation in patients with resected pancreatic carcinoma: a trial of the ECOG-ACRIN Cancer Research Group (E2204). J Surg Oncol. 2018;94(1):39–46.
31. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.
32. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
33. Reni M, Balzano G, Aprile G, Cereda S, Passoni P, Zerbi A, et al. Adjuvant PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) or gemcitabine followed by chemoradiation in pancreatic cancer: a randomized phase II trial. Ann Surg Oncol. 2012;19(7):2256–63.

34. Reni M, Balzano G, Zanon S, Zerbi A, Rimassa L, Castoldi R, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. Lancet Gastroenterol Hepatol. 2018;3(6):413–23.
35. Schmidt J, Abel U, Debus J, Harig S, Hoffmann K, Herrmann T, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol. 2012;30(33):4077–83.
36. Shimoda M, Kubota K, Shimizu T, Katoh M. Randomized clinical trial of adjuvant chemotherapy with S-1 versus gemcitabine after pancreatic cancer resection. Br J Surg. 2015;102(7):746–54.
37. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial. J Clin Oncol. 2017;35(29):3330–7.
38. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009;101(6):908–15.
39. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388(10041):248–57.
40. Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28(29):4450–6.
41. Yoshitomi H, Togawa A, Kimura F, Ito H, Shimizu H, Yoshidome H, et al. A randomized phase II trial of adjuvant chemotherapy with uracil/tegafur and gemcitabine versus gemcitabine alone in patients with resected pancreatic cancer. Cancer. 2008;113(9):2448–56.
42. Califf RM. Biomarker definitions and their applications. Exp Biol Med (Maywood, NJ). 2018;243(3):213–21.
43. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47–52.
44. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019;16(4):207–20.
45. The Cancer Genome Atlas Research Network. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017;32(2):185–203.e13.
46. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
47. Martinez-Useros J, Garcia-Foncillas J. The role of BRCA2 mutation status as diagnostic, predictive, and prognosis biomarker for pancreatic cancer. Biomed Res Int. 2016;2016:1869304.
48. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33(28):3124–9.
49. Iqbal J, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2012;107(12):2005–9.
50. Furuse J. Paradigm shifting of systemic chemotherapy for unresectable pancreatic cancer in Japan. J Clin Med. 2019;8(8):1170.
51. Navarro EB, López EV, Quijano Y, Caruso R, Ferri V, Durand H, et al. Impact of BRCA1/2 gene mutations on survival of patients with pancreatic cancer: a case-series analysis. Ann Hepatobiliary Pancreat Surg. 2019;23(2):200–5.
52. Sonnenblick A, Kadouri L, Appelbaum L, Peretz T, Sagi M, Goldberg Y, et al. Complete remission, in BRCA2 mutation carrier with metastatic pancreatic adenocarcinoma, treated with cisplatin based therapy. Cancer Biol Ther. 2011;12(3):165–8.

Chapter 9
Regionalization to Improve Outcomes in Pancreatic Surgery

Rachel V. Guest and Kjetil Søreide

Take Home Messages
- A volume-outcome relationship exists for pancreatic surgery.
- Higher volume may be an indicator for teaching level or academic institution.
- Regionalization/centralization of pancreatic surgery has been slow in most countries.

Pearls and Pitfalls
- Volume (e.g. number of procedures) is not sufficient to increase quality of care.
- Outcome is related to multiple factors of care—number of procedures is not enough.
- Quality is related to staff numbers, multidisciplinary teams and consistency in care.
- Different regions/countries may arrive at variable criteria for regionalization, based on economic, geographical and health service factors unique to each place.

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Future Perspectives

- Understanding barriers to regionalization is essential to better achieve response to desired political decisions.
- Outcomes should be monitored at the population level, rather than institutional numbers, to gauge true health effects for a given disease.
- Evaluation of composite measures such as the 'Textbook Outcome' should be considered as proxies for quality of care rather than individual metrics such as mortality.

9.1 Introduction

Centralization has been defined as the concentration of healthcare resources, including infrastructure, staff, materials, knowledge and research in order to improve quality of care and financial efficiency. The effect of a volume-outcome relationship and the consequent plea for centralization of complex procedures has been an ongoing debate for decades [1–4]. The debate does not concern so much the question of an existing effect or not from centralization—most would agree that there is a demonstrated effect-association between a higher number of procedures and better outcomes (such as reduced mortality), in particular for pancreatic surgery [5, 6]. Rather, as it were, debate concerns for the most part the way and how such regionalization should be done, based on what criteria and with what practical consequences [7, 8]. Obviously, much is at stake from several different perspectives, importantly including the patient, and the several stakeholders that express true or perceived barriers to fulfilling a regionalization process in most instances (Fig. 9.1). This chapter aims to present some of the ongoing issues with centralization of surgical care, and the benefits and barriers associated with this.

9.2 The Volume-Outcome Debate

One of the most debated topics in regionalization concerns that of volume (as in numbers of procedures), with several attempts at defining an "optimal" cut-off of procedures that should define acceptable practice. Several ideas and theories stem from this sometimes too simplistic look at volume-outcome association. However, it is now understood and agreed by consensus that a number for cut-off per se is not sufficient to ensure proper quality care in complex surgery [9], including pancreatic surgery for cancer. Rather a set of 12 recommendations have been put forward in a consensus [9] (Box 9.1).

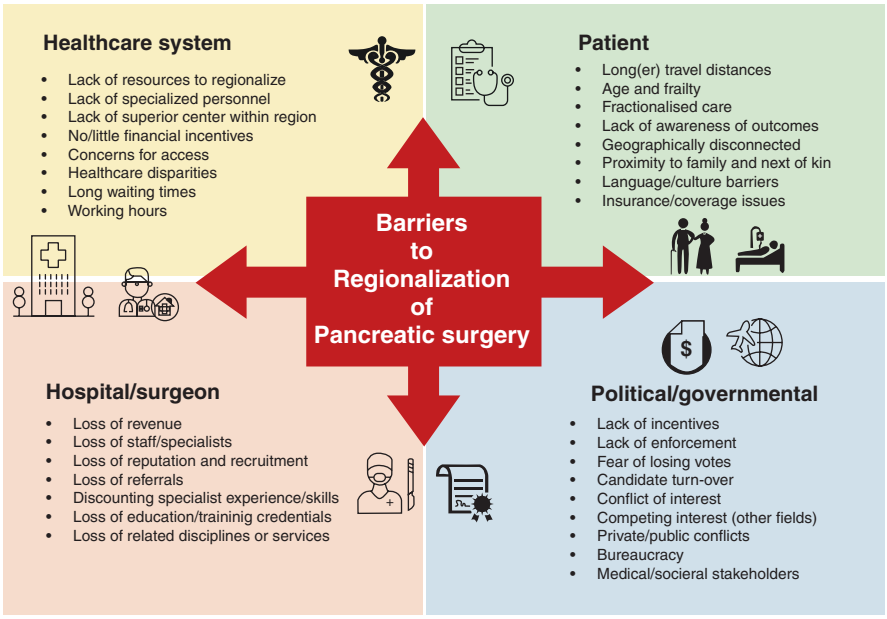

Fig. 9.1 Barriers to regionalization of surgery at various levels. Elements may play variable roles across different health care systems, explaining the difference in centralization policy and effects across countries

Box 9.1 Recommendations for Centralization

- Definition should be based on disease (e.g., pancreatic cancer) or on organ systems (e.g., complex HPB diseases) rather than a procedure (e.g., 'esophagectomy' or 'pancreatectomy').
- The planning is based on minimal numbers of cases per center and also well distributed among various regions, considering population and cultural specificities, in a country.
- Planning should include at least two centers per country to secure choice and competition (except for small countries and very rare diseases).
- Appropriate resources must be secured with proper evaluation of available infrastructure and personnel.
- Centers must offer fully functioning multidisciplinary teams (MDTs) of specialists capable of tackling all aspects of the diseases all the year around.
- Centers must be linked to a network of hospitals to secure adequate referral and follow-up.

- Specifications of centralization must be legally enforced for adherence to specifications applied at the local and regional level and for private and nonprivate hospitals.
- The process for centralization must be accompanied by mainstream media activities to secure appropriate awareness of the population.
- Centers must have an externally audited database and be actively involved in clinical studies (including RCTs) and should be encouraged to contribute to laboratory research along with basic scientists.
- Quality control must be accompanied by international benchmark comparative studies.
- Equal accessibility to centralized health care should be monitored.
- Centers must be involved in surgical education, and secure specialized training as well as allowing rotation of 'general surgeons'.

9.3 Measuring Quality of Care Beyond Simple Metrics

Traditionally, outcomes in cancer surgery have been measured using quantitated metrics such as mortality, morbidity, and readmission rates or oncological parameters including R_0 and recurrence rates [10]. However, it is recognized that from the patient's perspective such individual outcomes might not always be representative of a center's performance. A low event rate outcomes such as mortality can be insufficiently sensitive and centers may perform well in one area but badly in another [11].

Some groups have therefore suggested composite measures such as the 'Textbook Outcome' for a more global prediction of performance [12]. Textbook Outcome has been applied in pancreatic surgery to assess the effect of a hospital's status as a teaching centre on outcomes [13]. In this study of 8035 Medicare patients in the United States, Textbook Outcome was defined as the absence of complication, prolonged length of stay, readmission, or death and was achieved in 44.1% of patients undergoing pancreatic resection and was more likely to occur in a major teaching hospital and in high-volume (≥20 resections per year) centers.

The Dutch Pancreatic Cancer Group conducted a survey of 24 international experts to reach consensus on Textbook Outcome (Box 9.2) in pancreatic surgery and applied multivariate logistic regression to identify predictors using the Dutch Pancreatic Cancer Audit between 2014 and 2017 [14]. Importantly, and in contrast to other specialties, the Textbook Outcome in pancreatic surgery did not include any pathological parameters; consensus agreed that in contrast to other cancers, margin status in pancreatic cancer more frequently reflects the extent of pathological assessment and disease biology (more likely to be locally advanced) than in other resectable solid tumors. Of 3341 patients, (79% pancreatoduodenectomy, 21% distal pancreatectomy) Textbook Outcome was achieved in 60.3%. In pancreatoduodenectomy, Textbook Outcome was predicted by a dilated pancreatic duct (≥3 mm) and PDAC as indication for surgery. ASA class 3 was associated with risk of having a

Box 9.2 Proposed Definition of Textbook Outcome in Pancreatic Surgery

Defined as absence of
• Postoperative pancreatic fistula (ISGPS grade B/C)
• Bile leak
• Post-pancreatectomy haemorrhage
• Severe complication (Clavien Dindo grade ≥ III)
• In-hospital mortality

Based on definitions in the Dutch Pancreatic Cancer Audit [14]

worse Textbook Outcome. In patients undergoing distal pancreatectomy, female gender and the absence of neoadjuvant treatment predicted improved Textbook Outcome.

In the Netherlands, 18 out of the 20 centers performing pancreatic surgery perform ≥20 resections a year, with 5 centers performing ≥40 per year. Despite this high proportion of 'high volume' centers, there was considerable variation in Textbook Outcome between institutions even following case-mix adjustment, compounding the need for quality assurance programs and audit.

A number of limitations to the use of Textbook Outcomes have been highlighted, particularly in terms of evaluating quality of care following regionalization. Length of stay is often a major barrier to patients achieving Textbook Outcome [15]. There are frequently cultural, organizational and economic factors that heavily influence length of stay between countries, for example Asian centers frequently have longer length of stay than European or US centers. In one analysis, when length of stay was removed from the Textbook Outcome, Eastern hospitals went from exhibiting consistently lower rates of Textbook Outcomes than Western centers to consistently higher rates [16]. Textbook Outcomes are reliant on the variables and data quality of multi-institutional databases. Hence, factors such as patient satisfaction is rarely available. Notably, several studies have failed to demonstrate any association between Textbook Outcome and case-volume [16, 17].

9.4 Context over Numbers

Whilst a volume-outcome relationship has been frequently demonstrated in pancreatic surgery [18, 19] this relationship is still debated for several reasons; e.g. that centralization has not universally led to improved outcomes [20] or reduction of complications; others argue that low-volume institutions may produce comparable results to higher volume centres; that 'lower' volume definitions have changed and hence the volume-outcome relationship may be less prominent; and that case-mix and procedure-mix may balance the actual volumes [21–26]. Some argue that of all complex surgical procedures, pancreatic surgery most sensitively illustrates the volume-outcome relationship and exhibits the widest range in mortality rates

between high and low volume centers. And yet, in recent large-scale datasets, a clear association between volume and outcomes could not be established for pancreatic cancer in Sweden [27] (despite regionalization of care over the past decade). Furthermore, a volume-benefit could not be established beyond six pancreatic procedures in a further study from Sweden [28], in which the best predictor of outcome was status as 'teaching hospital'.

'Hospital status' serves as an indicator for hospitals with a more complex service with several disciplines available to handle complications [23, 25, 26], e.g. endoscopy, interventional radiology, intensive care and subdiscipline surgical services available 24 days a week, 365 days a year. This is supported by data from the Netherlands [29], Norway [30–32], and a study of 285,442 patients in the United States where patients undergoing HPB procedures had better outcomes at teaching hospitals, even among high-volume centers [33]. The findings from this Medicare-based US-population sample where the benefits seen in centers classified as 'teaching hospitals' (defined by dividing the aggregate number of interns and residents by the number of beds), however was lost on stratified analysis [13]. Patients undergoing surgery in a major teaching hospital were 29% more likely to achieve Textbook Outcome if the center was high volume, whereas among patients undergoing surgery in a high-volume center, Textbook Outcome was comparable between major and minor teaching hospitals. Dimick and colleagues similarly found the effects of teaching hospital status was explained by higher volume [34].

Notably, the registry-based studies are susceptible to confounders including bias due to selective referral and reporting to registries. In a nationwide study from Sweden the relationship between hospital teaching status and long-term outcomes using the comprehensive national Swedish registry which includes all citizens and links to emigration and death registries to ensure completeness of follow up [28]. For 3298 patients, hospital university teaching status was associated with reduced mortality more than 2 years after surgery. Such effects are likely to be due to contributions from factors including standardized patient selection, multidisciplinary team management, use of adjuvant therapies, consistent lymph node and vascular resection techniques, critical care and post-operative after care provision. As in other studies, lower hospital volume increased short-term but not long-term mortality.

9.4.1 Benefits from Anatomically Related Procedures and Outcomes

The effects of volume of individual surgeons rather than at the facility level have been less frequently studied, but in general studies uphold the principle that improved outcomes in mortality, complications and shorter hospital stay are observed with higher volume. Some studies have suggested that outcomes of medium volume surgeons can be similar to high volume surgeons when operating in high volume institutions. It may be that the benefits of high-volume institutions including reduced 'failure to rescue' phenomena compensate to some degree for low volume surgeons [35].

The additional surgery done by a surgeon (the operative mix) adds to the experience and ability to handle procedures, complications and be diligent in the anatomic area of interest. In an US National Inpatient Sample study on pancreatoduodenectomies, there were 1747 surgeons, of which 88.3% had low volume (≤5 pancreatoduodenectomies/year), 8.9% had moderate volume (6–16 pancreatoduodenectomies/year), and 2.8% had high volume (≥17 pancreatoduodenectomies/year) [36]. With added operative mix to pancreatic surgery (despite low volumes), volume was associated with decreased inpatient mortality, shorter hospital stay, and lower likelihood of any postoperative complication [36].

Hence, one should review the goal or regionalization of care. Is it to create a scenario for single-organ surgeons who would operate solely on one organ? Or, for a setting that includes a wider HPB spectrum? Should all procedures be offered in every center, such as arterial resections? A wider gastrointestinal surgical oncology spectrum and operative mix of procedures in the alimentary tract, such as gastric, liver, biliary, and pancreatic surgery is associated with favorable outcomes, even in the lower range volume of specific procedures [36].

9.4.2 Improved Outcomes over Time

Many have argued that the improvements observed in mortality over the last two decades have been due to improvements within, not between volume categories [37, 38]. The volume-outcome relationship has attenuated over time with the introduction of other improvements in perioperative care especially in low and medium volume centers, such as surgical checklists and public reporting of mortality rates. It has been shown that low volume centers frequently report only slightly higher complication rates, but the observed higher mortality and morbidity is frequently due to 'failure to rescue' [29, 39]. This is seen most often in centers with lower nurse-to-patient ratios, less ITU bed availability, understaffing, hierarchy and lack of support for junior staff. It is likely that in high volume centers all staff members including residents, nurses, critical care staff and interventional radiologists have more experience in the detection and management of major complications after pancreatic surgery. In summary, what is clear and reproducibly observed across all studies on this topic is that very low volume centers consistently report poorer outcomes [40].

9.4.3 Readmissions

In a study of almost ten million Medicare patients covering 12 surgical procedures [41], readmission to the index hospital was associated with a 26% lower risk of 90-day mortality than readmission to a non-index hospital. This effect was significant for all procedures in inverse probability-weighted models, and was largest for patients who were readmitted after pancreatectomy.

9.5 Current State of Regionalization

A systematic review of centralization of pancreatic surgery in Europe was recently presented [42]. The review by Polonski et al. [42] found that most countries that were included during the study period had failed to implement regionalization of pancreatic surgery, despite the majority of studies showing a survival benefit in higher volume hospitals. The lack of centralization is reported also in nationwide studies from France [43], Italy [44], Austria [45] and Germany [46].

9.5.1 Nordic Countries

In contrast to the lack of centralization in other parts of Europe, results for pancreatic surgery have been documented from Norway [30, 31], Finland [47] and Sweden [48]. In Norway (approx 5.5 mill.), both pancreatoduodenectomies [30] and distal resections [31] are currently done in five university hospitals with documented equal outcome across four regions of diverse population density, geographical distances, variable inhabitant numbers and actual number of procedures performed. Perioperative mortality rates are comparable to so-called 'ivory towers', with less than 2% 30-day mortality and 4% 90-day mortality [30]. Importantly, the *resection rates per population* is equal across all regions [30, 31], indicating an equal access to surgical services to the population. This fact is extremely important when debating outcomes, and particularly for pancreatic cancer.

9.5.2 Rest of Europe

In a study from England [49], there were 31,973 pancreatic cancer patients studied, 2580 had surgery (8.1%). Increasing resection rates were associated with lower mortality among all patients. Among patients that underwent surgery, higher procedure volume was associated with lower mortality in hospitals carrying out >30 versus <15 operations a year [49].

In the western part of the Netherlands where centralization of pancreatic surgery occurred in 2006, improvements in survival have been observed [50]. In this relatively small cohort, a greater proportion of patients received surgical treatment for pancreatic cancer following centralization (14.3–18.4%) and no increase in waiting times were seen. Such results were reinforced by a nationwide study of patients undergoing pancreatoduodenectomy in the Netherlands between 2004 and 2009, during which time the proportion of patients undergoing surgery in a medium or high-volume center increased from 53 to 91% (medium defined as 11–19 and high volume as ≥20 procedures per year). The mortality rate during the 6-year period was 14.7%, 9.8%, 6.3% and 3.3% in very low-, low-, medium- and high-volume hospitals respectively [51].

Data from Germany has demonstrated that despite the accumulating evidence in favor of high volumes hospitals, a substantial proportion of pancreatic surgery is still performed in low volume centers. A comprehensive nationwide snapshot of all patients undergoing a pancreatic operation in Germany between 2009 and 2013 revealed an overall in-hospital mortality rate of 10.1%; significantly and concerningly higher than previously published German single and multi-institution studies [52]. This reveals the clear publication bias inherent in the field and highlights the lack of enforcement of minimum caseload requirements, which were brought into German law in 2004 (49% of hospitals were performing less than the required number of minimum procedures).

9.5.3 "Take the Volume Pledge" in the United States

Due to the high number of pancreatectomies done in low volume hospitals in the United States, three payers came together in 2015 to suggest minimum requirement volumes for hospitals in order to increase quality [53]. Upon modelling the current situation, it has become clear that access may become a major issue for a considerable number of patients, if a majority of procedures were to shift to high volume centers. Concerns about access to care has thus emerged [54, 55]. Importantly there is evidence that such inequalities in access differentially affect black and ethnic minority patients, patients from low socioeconomic backgrounds and patients without health insurance [56, 57]. There are likely a number of reasons for this, including a lack of publicly available volume data, particularly to patients with low health literacy, which could be addressed. Continuing regionalization without addressing such health inequalities is likely to widen existing disparities [58–61].

9.6 Barriers to Regionalization

The reasons why a large proportion of countries have failed to implement centralization of pancreatic surgery are multifactorial and complex (Fig. 9.1). Quality of care at an acceptable financial and political cost is the goal of all healthcare systems, however different nations have differing healthcare, political and financial pressures which result in patient outcomes not always lying at the center of organizational processes.

The implementation of regionalizing surgical services has varied hugely between countries as well as between specialties and the delivery of gastrointestinal surgery in particular, has remained fragmented in most nations. A legion of reasons are behind this, and although the contrast with specialties such as neurosurgery and transplantation is in some part accounted for by historical structural differences in funding, expertise and political interests, the spread of the provision of pancreatic surgery remains wide despite evidence for the volume-outcome relationship and the

introduction of legally binding volume thresholds. The barriers to centralization can be broadly grouped into four principal categories:

9.6.1 The Patient

One criticism of centralization is that many patients would face increased travel burdens if obligated to travel to higher volume centers or teaching hospitals for cancer care and that this burden disproportionately affects vulnerable patient groups. It is established that the public use of healthcare falls with increasing distance to providers [62]. Data from the United States where this issue is most burdensome suggests however that longer distances are not necessarily inevitable for many patients and indeed, 25% of Medicare patients undergoing pancreatectomy already lived *closer* to a higher volume hospital [62]. This study found that the majority (74%) of patients would add less than 30 min of extra travel time to their journey to reach a center performing >16 pancreatectomies per year. These data are mirrored in studies from Europe where a significant amount of 'hospital bypassing' is already observed [63]. This also raises the issue as to whether perioperative care including radiological services, biliary drainage and oncology services should be restricted to higher volume centers or whether some, or all of this care can be received in spoke/networked hospitals. Furthermore, it remains of some debate as to whether publicly available and accessible data yet exist to allow patients to make truly informed decisions about selecting healthcare in this way.

9.6.2 Healthcare Systems

A strong evidence base for the volume-outcome relationship has been insufficient for physicians to initiate change in practice autonomously and implement centralization. In esophageal cancer, a combination of scientific evidence and regulation of required minimum volumes was necessary to effect true centralization of services in the Netherlands [64]. The impact of pressure from the Dutch Health Inspectorate was seen in 2006 after introducing a requirement for ten procedures per year and a further centralizing effect followed in 2011 when insurers introduced minimum volume thresholds into negotiations for reimbursements with hospitals. In public systems where services are funded by central government via local health boards, it may be that true regionalization will not occur until central funding is withdrawn from low volume centers. Networked hospitals performing low volume surgery have continued to apply pressure to retain services locally, citing lack of resources, specialized personnel or lack of an existing regional specialist center as barriers to implementation. Furthermore, disparities in access including longer waiting times and availability, especially for rural populations, continue to be raised as politically sensitive arguments for maintaining de-centralized pancreatic services.

9.6.3 Hospital/Surgeon

The consequences of centralized pancreatic surgery naturally have profound implications for individual surgeons practicing in low-volume centers. Professional pride, reputation, fiscal implications following loss of referrals, training and recruitment of surgeons and other staff, including those in adjuvant services including endoscopy and radiology are all at risk from the loss of specialized cancer services. Surgeons who have followed prolonged training routes and pursued subspecialty fellowships are understandably reluctant to relinquish the skills and experience they have accumulated. Moreover, the perceived repercussions on the reputation and standing of institutions as training and academic centers should not be underestimated and have meant that hospitals have supported surgeons' ongoing provision of pancreatic cancer surgery, even in very low-volume units. Conversely, surgeons in peripheral, 'at-risk' centers complain that such structural changes are frequently driven by commissioners and practitioners in high-volume hospitals and thereby point out the similar conflicts of interest posed by such drives towards re-organization [9].

9.6.4 Political/Government

The introduction of legally binding volume requirements has not occurred in the majority of countries, principally because few data exist regarding exact thresholds for procedure numbers. As we have already seen however, where such regulations have been instigated, these have not always been legally enforced and have not necessarily driven regionalization forward. Frequently provision and the ongoing support of local health services especially in rural communities, boosts voting in local government elections and politicians have frequently campaigned to continue funding of regional intensive care and other services in pursuit of office. In countries where the public and private health services co-exist, it is not uncommon that centralization has been implemented to at least some degree in the public sector but is not mandated by private clinics. Further healthcare and societal research are required to better understand the competing pressures that continue to supersede the evidence supporting better outcomes in pancreatic surgery in centralized systems.

9.7 Conclusion

A heavy centralization may boost volumes and outcomes in large centers but may not necessarily ensure that the population at risk is offered equal access to care. The process of centralization (or, regionalization) of care should also take into account the complexity of services provided. The need for single-organ surgeons or broadly trained HPB surgeons or even surgical oncologist may largely vary dependent on the region, population density and health care systems.

Pancreatic cancer remains a formidable health burden for which surgery represents but one treatment modality that is not easily measured in isolation. Simple questions usually have simple answers. Complex questions usually have complex solutions, which are doable but not necessarily easily solved.

References

1. Gouma DJ, Obertop H. Centralization of surgery for periampullary malignancy. Br J Surg. 1999;86:1361–2.
2. Soreide K, Nymo LS, Lassen K. Centralization of pancreatic surgery in Europe: an update. J Gastrointest Surg. 2019;23:2322–3.
3. Massoumi RL, Hines OJ. Aggregating pancreatic cancer care to specialized centers—a high-value decision? JAMA Surg. 2019;154(10):e193020.
4. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med. 1979;301:1364–9.
5. Tol JA, van Gulik TM, Busch OR, et al. Centralization of highly complex low-volume procedures in upper gastrointestinal surgery. A summary of systematic reviews and meta-analyses. Dig Surg. 2012;29:374–83.
6. Gooiker GA, van Gijn W, Wouters MW, et al. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg. 2011;98:485–94.
7. Gagliardi AR, Soong D, Gallinger S. Identifying factors influencing pancreatic cancer management to inform quality improvement efforts and future research: a scoping systematic review. Pancreas. 2016;45:161–6.
8. Mohammed S, Fisher WE. Quality metrics in pancreatic surgery. Surg Clin North Am. 2013;93:693–709.
9. Vonlanthen R, Lodge P, Barkun JS, et al. Toward a consensus on centralization in surgery. Ann Surg. 2018;268:712–24.
10. Graham LA, Mull HJ, Wagner TH, et al. Comparison of a potential hospital quality metric with existing metrics for surgical quality-associated readmission. JAMA Netw Open. 2019;2:e191313.
11. Dimick JB, Staiger DO, Baser O, et al. Composite measures for predicting surgical mortality in the hospital. Health Aff (Millwood). 2009;28:1189–98.
12. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. JAMA. 2006;295:1168–70.
13. Mehta R, Paredes AZ, Tsilimigras DI, et al. Influence of hospital teaching status on the chance to achieve a textbook outcome after hepatopancreatic surgery for cancer among Medicare beneficiaries. Surgery. 2020;168(1):92–100.
14. van Roessel S, Mackay TM, van Dieren S, et al. Textbook outcome: nationwide analysis of a novel quality measure in pancreatic surgery. Ann Surg. 2020;271:155–62.
15. Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, et al. Textbook outcome as a composite measure in oesophagogastric cancer surgery. Br J Surg. 2017;104:742–50.
16. Merath K, Chen Q, Bagante F, et al. A multi-institutional international analysis of textbook outcomes among patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma. JAMA Surg. 2019;154:e190571.
17. Levy J, Gupta V, Amirazodi E, et al. Gastrectomy case volume and textbook outcome: an analysis of the Population Registry of Esophageal and Stomach Tumours of Ontario (PRESTO). Gastric Cancer. 2020;23:391–402.
18. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346:1128–37.

19. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. JAMA. 1998;280:1747–51.
20. Williamsson C, Ansari D, Andersson R, et al. Postoperative pancreatic fistula-impact on outcome, hospital cost and effects of centralization. HPB (Oxford). 2017;19:436–42.
21. El Amrani M, Clement G, Lenne X, et al. Failure-to-rescue in patients undergoing pancreatectomy: is hospital volume a standard for quality improvement programs? Nationwide analysis of 12,333 patients. Ann Surg. 2018;268:799–807.
22. Bateni SB, Olson JL, Hoch JS, et al. Drivers of cost for pancreatic surgery: it's not about hospital volume. Ann Surg Oncol. 2018;25:3804–11.
23. Wilson GC, Geller DA. Facility type is another factor in the volume-outcome relationship for complex hepatopancreatobiliary procedures. Ann Surg Oncol. 2019;26:3811–2.
24. Wasif N, Etzioni DA, Habermann EB, et al. Does improved mortality at low- and medium-volume hospitals lead to attenuation of the volume to outcomes relationship for major visceral surgery? J Am Coll Surg. 2018;227:85–93.e9.
25. Brown EG, Bateni SB, Burgess D, et al. Interhospital variability in quality outcomes of pancreatic surgery. J Surg Res. 2019;235:453–8.
26. Haneuse S, Dominici F, Normand SL, et al. Assessment of between-hospital variation in readmission and mortality after cancer surgical procedures. JAMA Netw Open. 2018;1:e183038.
27. Gottlieb-Vedi E, Mattsson F, Lagergren P, et al. Annual hospital volume of surgery for gastrointestinal cancer in relation to prognosis. Eur J Surg Oncol. 2019;45(10):1839–46.
28. Derogar M, Blomberg J, Sadr-Azodi O. Hospital teaching status and volume related to mortality after pancreatic cancer surgery in a national cohort. Br J Surg. 2015;102:548–57; discussion 557.
29. van Rijssen LB, Zwart MJ, van Dieren S, et al. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit. HPB (Oxford). 2018;20:759–67.
30. Nymo LS, Soreide K, Kleive D, et al. The effect of centralization on short term outcomes of pancreatoduodenectomy in a universal health care system. HPB (Oxford). 2019;21:319–27.
31. Soreide K, Olsen F, Nymo LS, et al. A nationwide cohort study of resection rates and short-term outcomes in open and laparoscopic distal pancreatectomy. HPB (Oxford). 2019;21(6):669–78.
32. Soreide K, Nymo LS, Kleive D, et al. Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system. Pancreatology. 2019;19:880–7.
33. Hyder O, Sachs T, Ejaz A, et al. Impact of hospital teaching status on length of stay and mortality among patients undergoing complex hepatopancreaticobiliary surgery in the USA. J Gastrointest Surg. 2013;17:2114–22.
34. Dimick JB, Cowan JA Jr, Colletti LM, et al. Hospital teaching status and outcomes of complex surgical procedures in the United States. Arch Surg. 2004;139:137–41.
35. Harmon JW, Tang DG, Gordon TA, et al. Hospital volume can serve as a surrogate for surgeon volume for achieving excellent outcomes in colorectal resection. Ann Surg. 1999;230:404–11; discussion 411–3.
36. Hachey K, Morgan R, Rosen A, et al. Quality comes with the (anatomic) territory: evaluating the impact of surgeon operative mix on patient outcomes after pancreaticoduodenectomy. Ann Surg Oncol. 2018;25:3795–803.
37. Learn PA, Bach PB. A decade of mortality reductions in major oncologic surgery: the impact of centralization and quality improvement. Med Care. 2010;48:1041–9.
38. Wasif N, Etzioni D, Habermann EB, et al. Contemporary improvements in postoperative mortality after major cancer surgery are associated with weakening of the volume-outcome association. Ann Surg Oncol. 2019;26:2348–56.
39. Sheetz KH, Dimick JB, Ghaferi AA. Impact of hospital characteristics on failure to rescue following major surgery. Ann Surg. 2016;263:692–7.
40. Ahola R, Sand J, Laukkarinen J. Centralization of pancreatic surgery improves results: review. Scand J Surg. 2020;109:4–10.

41. Brooke BS, Goodney PP, Kraiss LW, et al. Readmission destination and risk of mortality after major surgery: an observational cohort study. Lancet. 2015;386:884–95.
42. Polonski A, Izbicki JR, Uzunoglu FG. Centralization of pancreatic surgery in Europe. J Gastrointest Surg. 2019;23:2081–92.
43. Farges O, Bendersky N, Truant S, et al. The theory and practice of pancreatic surgery in France. Ann Surg. 2017;266:797–804.
44. Balzano G, Guarneri G, Pecorelli N, et al. Modelling centralization of pancreatic surgery in a nationwide analysis. Br J Surg. 2020; in press. https://doi.org/10.1002/bjs.11716.
45. Cardini B, Primavesi F, Maglione M, et al. Outcomes following pancreatic resections—results and challenges of an Austrian university hospital compared to nationwide data and international centres. Eur Surg. 2019;51:81–9.
46. Krautz C, Nimptsch U, Weber GF, et al. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg. 2018;267:411–7.
47. Antila A, Ahola R, Sand J, et al. Management of postoperative complications may favour the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012-2014. Pancreatology. 2019;19:26–30.
48. Tingstedt B, Andersson B, Jonsson C, et al. First results from the Swedish National Pancreatic and Periampullary Cancer Registry. HPB (Oxford). 2019;21:34–42.
49. Coupland VH, Konfortion J, Jack RH, et al. Resection rate, hospital procedure volume and survival in pancreatic cancer patients in England: population-based study, 2005-2009. Eur J Surg Oncol. 2016;42:190–6.
50. Gooiker GA, van der Geest LG, Wouters MW, et al. Quality improvement of pancreatic surgery by centralization in the western part of the Netherlands. Ann Surg Oncol. 2011;18:1821–9.
51. de Wilde RF, Besselink MG, van der Tweel I, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg. 2012;99:404–10.
52. Nimptsch U, Krautz C, Weber GF, et al. Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. Ann Surg. 2016;264:1082–90.
53. Urbach DR. Pledging to eliminate low-volume surgery. N Engl J Med. 2015;373:1388–90.
54. Schwartz DM, Fong ZV, Warshaw AL, et al. The hidden consequences of the volume pledge: "no patient left behind"? Ann Surg. 2017;265:273–4.
55. Blanco BA, Kothari AN, Blackwell RH, et al. "Take the volume pledge" may result in disparity in access to care. Surgery. 2017;161:837–45.
56. Wasif N, Etzioni D, Habermann EB, et al. Racial and socioeconomic differences in the use of high-volume commission on cancer-accredited hospitals for cancer surgery in the United States. Ann Surg Oncol. 2018;25:1116–25.
57. Liu JH, Zingmond DS, McGory ML, et al. Disparities in the utilization of high-volume hospitals for complex surgery. JAMA. 2006;296:1973–80.
58. Bateni SB, Gingrich AA, Hoch JS, et al. Defining value for pancreatic surgery in early-stage pancreatic cancer. JAMA Surg. 2019;154:e193019.
59. Chhabra KR, Dimick JB. Strategies for improving surgical care: when is regionalization the right choice? JAMA Surg. 2016;151:1001–2.
60. Diaz A, Pawlik TM. Optimal location for centralization of hospitals performing pancreas resection in California. JAMA Surg. 2019;155(3):261–3.
61. Gold JS. Linking disparities to outcomes in pancreatic cancer: inching toward answers. JAMA Surg. 2020;155(2):e195082.
62. Goodman DC, Fisher E, Stukel TA, et al. The distance to community medical care and the likelihood of hospitalization: is closer always better? Am J Public Health. 1997;87:1144–50.
63. Versteeg SE, Ho VKY, Siesling S, et al. Centralisation of cancer surgery and the impact on patients' travel burden. Health Policy. 2018;122:1028–34.
64. Kilsdonk MJ, Siesling S, van Dijk BAC, et al. What drives centralisation in cancer care? PLoS One. 2018;13:e0195673.

Chapter 10
Oncopolitics in Pancreatic Cancer

Peter Naredi and Tit Albreht

Take Home Messages

- "Europe's beating cancer plan" by the European Commission (EU) has a central role in creating resources for pancreatic cancer care and research.
- In Europe the EU project Innovative Partnership for Action Against Cancer (iPAAC) Joint Action focus on neglected cancers, especially pancreatic cancer.
- The Recalcitrant Cancer Research Act in US has increased federal funding for pancreatic cancer research.
- Several pancreatic cancer advocacy groups in Europe and US have aligned with governmental bodies to increase awareness and research funding.

Pearls and Pitfalls

- Several good initiatives to support care and research on pancreatic cancer is underway in both Europe and US.
- Patients with pancreatic cancer are now supported by organisations and politicians to increase awareness about the disease and urgently needed actions.
- The extremely dismal outcome, fatigue and short expected survival for patients with pancreatic cancer continuous to keep patients out of active participation in oncopolicy work.

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Future Perspectives

- During recent years it has become evident for politicians and funding bodies that pancreatic cancer research and care of patients with the disease must get much better support.
- Initiatives taken in e.g. the EU iPAAC Joint action and the US Recalcitrant Cancer Research Act should serve as models for future actions needed.
- Advances in the understanding of cancer biology and cancer metabolism as well as new treatment options in oncology must be implemented in the research agenda for pancreatic cancer.
- Pancreatic cancer must be a prioritized tumour type for funding of clinical studies.

10.1 Introduction

Pancreatic cancer is the deadliest cancer we know of. It is among the ten most common cancers in Europe and in the US and it is the cancer type ranked third by the number of deaths in Europe [1] and soon second in the US [2]. Progress has been limited with few overall clinical impacts over the past decades.

Unfortunately, public knowledge and awareness of subtle and dire symptoms is limited for this cancer form. Citizens, as well as politicians and other stakeholders know very little about pancreatic cancer per se. Pancreatic cancer has not until recently been prioritized but instead it has been a neglected tumour type. While other cancer types have galas, media events and fundraiser campaigns to raise awareness and funding to strengthen research and care, this has been neglected in pancreatic cancer.

In order to improve public awareness, funding priorities to enhance research, trials and clinical care there is a need for directed oncopolitics. This chapter will highlight the important areas to drive oncopolitics in pancreatic cancer.

Box 10.1 Definition of Oncopolicy

The word ‘oncopolicy’ is used to describe a sustained action to interact with politicians and other stakeholders, which should promote the cause of a certain task in cancer care. The word has mainly been used for interaction at EU level but is of course also true for actions at any European, global or national level.

10.2 Ongoing Oncopolicy Initiatives

There have been initiatives by individuals and cancer organisations/societies for decades but in Europe a roadmap for joint and sustained actions was set out by the European Cancer Organisation (ECCO) in 2009. This was to ensure that actions aimed at fighting cancer was a top priority of EU health and research policy agenda. At the first Oncopolicy Forum a European Academy of Cancer Sciences was created to influence EU politicians to strengthen European cancer research by increased funding and to create a European cancer research body, similar to the National Institute of Health, NIH, in the US.

The focus of ECCO Oncopolicy has widened to promote policies to underpin the multi-professionality in cancer care, and to provide broad responses to shape policymaking in common areas of concern across the cancer continuum. Topics of priority are treatment and care matters, organisation of cancer services, quality assurance and the oncology workforce. Much of this is to level out the inequalities we see in cancer care (for pancreatic cancer see; [3]), to prepare for the demographic "time bomb" with substantial more cancer cases due to an elderly population, and to allocate resources for access to innovations in cancer care [4].

Organisations important to shape European Oncopolicy are the patient advocacy groups, which have direct access to EU politicians and often work together with EU Members of parliament (MEP) in different cancer initiatives. They do this together with the European Cancer Leagues (ECL) and not-for-profit organisations of health care professionals, e.g. ECCO, European Society for Surgical Oncology (ESSO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Medical Oncology (ESMO).

Box 10.2 Organisations Involved in Pancreatic Cancer Oncopolitics

European Cancer Leagues (ECL	https://www.europeancancerleagues.org/
European Cancer organisation (ECCO)	https://www.ecco-org.eu/
European Society for Surgical Oncology (ESSO)	https://www.essoweb.org/
European Society for Radiotherapy and Oncology (ESTRO)	https://www.estro.org/
European Society of Medical Oncology (ESMO)	https://www.esmo.org/
European Cancer Concord	https://www.europeancancerconcord.eu/
EU MEPs Against Cancer (MAC)	https://www.europeancancerleagues.org/meps-against-cancer-about-meps-against-cancer-2/
Pancreatic Cancer Action	https://pancreaticcanceraction.org/
Pancreatic Cancer Europe	https://www.pancreaticcancereurope.eu/
Digestive Cancers Europe (DiCE)	https://digestivecancers.eu/
United European Gastroenterology (UEG)	https://www.ueg.eu/home/
Pancreatic Cancer Action Network (PanCAN)	https://www.pancan.org/
Lustgarten Foundation	https://www.lustgarten.org/

Another initiative is the European Cancer Concord (now part of ECCO) which was established by leading European cancer professionals and patient representatives. They launched and promoted the "The European cancer patient's bill of rights" [5] and have a vision 70:35 which is to achieve 70% long-term survival for cancer patients by 2035. Since 2005, there is a group of members of the parliament at EU with special interest in cancer policy, who are organized in MEPs Against Cancer (also known as MAC). Early 2019 they published a manifesto: Beating cancer: Mission possible—toward effective cancer control in Europe [6].

10.3 European Commission Initiated Actions in Cancer Health and Research

In 2009, the EU Commission adopted its Communication on Action Against Cancer with the European Partnership Against Cancer (EPAAC) and through a Joint Action (JA), launched in 2011, the purpose was to engage in a collaborative effort to tackle cancer more evenly and across Europe. One important aim was to get integrated and comprehensive national cancer plans in all EU member states and this is now in place in almost all European Union Member States [7]. EPAAC produced a Guide for the production of Quality National Cancer Control Plans/Programmes (NCCPs) [8]. In 2014, EPAAC ended and it was then followed by the next Joint Action, CANCON, which produced a guide for improving the quality of comprehensive cancer control [9]. Then in 2017 CANCON closed and since 2018 the Innovative Partnership for Action Against Cancer (iPAAC) Joint Action [10] builds upon deliverables in EPAAC and CANCON JAs and to implement innovative approaches to cancer control. Importantly, iPAAC should also focus on how to get better efficacy in dealing with neglected cancers, especially pancreatic cancer.

Box 10.3 Commission Communication on Action Against Cancer

Joint action	Years	Website
European Partnership Against Cancer (EPAAC)	2011–2014	http://www.epaac.eu/
CANCON	2014–2017	https://cancercontrol.eu/archived/index-2.html
Innovative Partnership for Action Against Cancer (iPAAC)	2018–ongoing	https://www.ipaac.eu/

There has been an EU Commission Expert Group on Cancer Control, including representatives from the EU commission, member states, patient and health professional organisations. This group was terminated before it really had any impact on cancer care.

Cancer is by the new EU Commissioner for Research, Science and Innovation, Carlos Moedas, considered as one of five great challenges facing our world and thus in 2019 a Mission assembly for cancer with leading cancer experts has been set up. This Mission will be part of Horizon Europe, the next EU research and innovation programme (2021–2027).

The former EU Commissioner for Health and Food safety, Vytenis Andriukaitis, was deeply involved in cancer issues and mainly with focus on preventive actions but in general the Juncker Commission unfortunately looked at health issues as rather peripheral in the EU agenda. There is hope that the new Commissioner with a history in the cancer community and with strong support of the President of the Commission will have more influence. The mission letter to Commissioner Kyriakides is specific with focus on supply of affordable medicines, the implementation of new regulatory framework on medical devices, the creation of a European Health Data Space, the implementation of an action plan on antimicrobial resistance, better communication on vaccination, food safety and least but very important the development of a "Europe's beating cancer plan". The Commissioner should work closely with the Commissioner for Research, science and innovations.

10.3.1 Oncopolicy for Pancreatic Cancer

With clear indications that cancer care and health research are moving into a more central role of the EU Commission it will be important to put key questions regarding pancreatic cancer in the spotlight. With the special focus on pancreatic cancer in the iPAAC Joint Action an important step forward is taken.

As mentioned above, the EU Commission's initiative to improve cancer care are Joint Actions and in the third and ongoing, iPAAC, the Roadmap for implementation and sustainability of the current and previous JA recommendations is being developed. The iPAAC Joint Action should focus on how to improve efficacy in dealing with neglected cancers, and specifically pancreatic cancer. New key indicators to assess clinical pathways and costs related to cancer and its interventions should be developed. This means that further development of cancer prevention, approaches to the use of genomics in cancer control, cancer information and registries, improvements and challenges in cancer care, surveys of innovative cancer treatments, governance of integrated cancer control including a new analysis of National Cancer Control Plans are now topics on the agenda that will be instrumental also for solutions for pancreatic cancer.

The impact of the reimbursement system is one of the questions that should be investigated within the framework of a cancer plan. The tasks of the iPAAC JA are split into different work packages. The aim of one work package is to define strategies to improve the quality of cancer care by optimizing the use of healthcare resources and promoting realistic and evidence-based responses to existing needs. The JA should raise awareness within the EU Policy and Research agenda. One

specific aim is to review and assess the situation for pancreatic cancer, highlighting the challenges and opportunities for improving detection, diagnosis, and access to expert clinicians in order to increase the quality of care and outcomes.

From the perspective of Oncopolicy, one key element in this effort is the reimbursement system for new technologies and treatments. Reimbursement mechanisms are essential components in addressing the introduction of new and expensive technologies. Pay-for-performance, bundled payments, and coverage with evidence development are alternatives, which in combination with more traditional reimbursement approaches, could both promote or discourage innovation. Most research focus is on new drugs but there is a need to review the different models implemented in therapeutic strategies so that radiation oncology and complex cancer surgery will not be pushed aside due to reimbursement practices in cancer care.

10.4 Action Plans to Increase Awareness of Pancreatic Cancer

Some tumour types, like breast cancer and prostate cancer, get much higher attention. Awareness of these tumour types is relatively high in the society and among politicians. This is not the case for pancreatic cancer, for which a vast majority of the citizens in Europe and US know almost nothing about the disease or its symptoms. It is not commonly known that pancreatic cancer is one of the ten most common tumour types and that over 90% of patients diagnosed with pancreatic cancer will die from the disease within 5 years. Nor are the signs/symptoms of pancreatic cancer well known. So, while thousands of cancer survivors of other tumour types are organized in strong patient advocacy groups this is not the case for pancreatic cancer. Still, some pancreatic cancer survivors have engaged with family members and volunteers in patient advocacy groups and pancreatic cancer organizations.

10.4.1 Pancreatic Cancer Action

Pancreatic Cancer Action [11] is an UK based charity which focuses on improving survival rates through early diagnosis of pancreatic cancer. In a recent survey they found that 95% of the UK population do not know what the symptoms of pancreatic cancer are. To raise awareness, they have a Pancreatic cancer Aware campaign and participate in the Pancreatic cancer awareness month, which is November. One day in November is the World pancreatic cancer day when the World pancreatic cancer coalition [12] consisting of more than 80 organisations from over 30 countries and six continents raise global awareness about pancreatic cancer.

10.4.2 Pancreatic Cancer Europe

Another European organisation based in Brussels is Pancreatic Cancer Europe [13], which recently became an associated partner of iPAAC. It is a multi-stakeholder platform to bring together experts from all of Europe including academics, physicians, politicians, patient groups, journalists and industry with a common interest to improve care for patients with pancreatic cancer.

10.4.3 Digestive Cancers Europe

A strong and established patient advocacy group for patients with colorectal cancers were EuropaColon. During a number of years this organization also took responsibility to represent other gastrointestinal tumours where the patient influence was weak. Thus it was a natural step when EuropaColon in 2018 transformed into Digestive Cancers Europe, DiCE, [14] also representing and giving voice to patients with pancreatic cancer. DiCE mission is to contribute to early diagnosis and decreased mortality from digestive cancers and to increase overall survival and quality of life.

10.4.4 United European Gastroenterology

United European Gastroenterology (UEG) published a special report on pancreatic cancer in 2018, “Pancreatic cancer across Europe”. It is a report of the past, present and future prospects of pancreatic cancer and the purpose is to enlighten European politicians about the needs for more research, better treatments and care (Pancreatic Cancer Across Europe: Taking a united stand. UEG, 2018, Fig. 10.1).

10.4.5 Pancreatic Cancer Action Network

In the US, the charity Pancreatic Cancer Action Network [15], PanCAN, funds research, provides patient/caregiver support, conducts community outreach and advocates for increased federal research funding for those affected by pancreatic cancer. Another US based organization is the Lustgarten Foundation [16], which is the largest private funder of pancreatic research. Their website has information on clinical trials, and they promote patients with pancreatic cancer to participate in these trials. To raise money for research and to increase awareness of pancreatic cancer PanCAN and Lustgarten Foundation arrange “PurpleStride—the walk to end pancreatic cancer” [17] in 55 cities across the US with more than 80,000 participants.

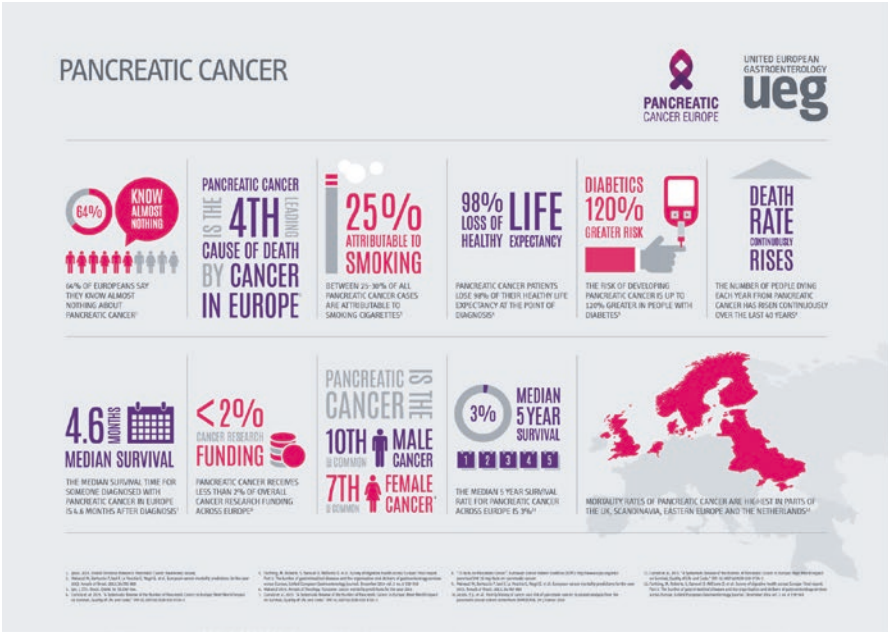

Fig. 10.1 Pancreatic cancer across Europe by UEG. Reproduced from UEG web site (https://www.ueg.eu/press/releases/ueg-press-release/article/pancreatic-cancer-set-to-become-third-biggest-cancer-killer-in-eu-next-year/). (With permission from UEG)

10.5 Research and Funding

In ClinicalTrials.org [18] there are almost 200 phase III trials registered for pancreatic cancer and this is at the top of gastrointestinal cancer diseases. Among them, 35 are still open for recruitment. Most of them are chemotherapy, targeted drugs or immunotherapy trials but there are also a few looking at innovative surgical techniques or devices or at radiotherapy.

The most frequent funder of interventional trials when the search word "pancreatic cancer" (n = 2424 hits) was used at ClinicalTrials.org is NIH with 424 trials. For Europe there are data from the National Cancer Research Institute (NCRI) [19] in UK and in 2009 less than 2% of cancer research funding went to research related to pancreatic cancer while it increased to 5% in 2017. This is similar to how much pancreatic cancer research received from NCI/NIH in the US in 2009 (2%) and despite the Recalcitrant Cancer Research Act it is still only 3% of NCI total budget of 5.6 billion USD in 2017.

The Recalcitrant Cancer Research Act (RCRA) [20] of 2012 require the Director of the NCI to develop a scientific framework for research on recalcitrant cancers (cancer with a 5-year relative survival rate below 50%), which includes: a review of

the status of research, such as a summary of findings, identification of promising scientific advances, a description of the availability of qualified scientific researchers, and the identification of resources available to facilitate research; identification of research questions that have not been adequately addressed; and recommendations for actions to advance research and for appropriate benchmarks to measure progress on achieving such actions. PanCAN lead the advocacy efforts to have pancreatic cancer included in the RCRA and this is one reason for the 70% increase in NCI funding for pancreatic cancer research since 2012 [21].

10.6 Conclusion

Several pancreatic cancer advocacy groups in Europe and US have aligned with governmental bodies to increase awareness and research funding. Good initiatives are underway in both Europe and US. It is important that the "Europe's beating cancer plan" by the European Commission (EU) prioritizes resources for pancreatic cancer care and research. Already the EU iPAAC) Joint Action focus on neglected cancers, especially pancreatic cancer and in the US the Recalcitrant Cancer Research Act has increased federal funding for pancreatic cancer research.

References

1. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol. 2016;55(9–10):1158–60.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
3. Pancreatic Cancer Europe. [Inequality report]. https://www.pancreaticcancereurope.eu/campaign/the-pancreatic-cancer-europe-inequality-report/.
4. Aapro M, Astier A, Audisio R, Banks I, Bedossa P, Brain E, et al. Identifying critical steps towards improved access to innovation in cancer care: a European CanCer Organisation position paper. Eur J Cancer. 2017;82:193–202.
5. Hojgaard L, Lowenberg B, Selby P, Lawler M, Banks I, Law K, et al. The European Cancer Patient's Bill of Rights, update and implementation 2016. ESMO Open. 2016;1(6):e000127.
6. Beating cancer: mission possible—toward effective cancer control in Europe. https://www.europeancancerleagues.org/mac-manifesto-2019/.
7. EPAAC. http://www.epaac.eu/home.
8. Albreht T, Martin-Moreno J, Jelenc M, Gorgojo L, Harris M. European guide for quality national cancer control programmes. Ljubljana: National Institute of Public Health; 2015.
9. CANCON. https://cancercontrol.eu/archived/who-we-are/index.html.
10. iPAAC. https://www.ipaac.eu/.
11. Pancreatic Cancer Action. https://pancreaticcanceraction.org/.
12. World Pancreatic Cancer Day. http://www.worldpancreaticcancerday.org/#.
13. Pancreatic Cancer Europe. https://www.pancreaticcancereurope.eu/.

14. DiCE. https://digestivecancers.eu/.
15. PanCAN. https://www.pancan.org/.
16. Lustgarten Foundation. https://www.lustgarten.org/.
17. PurpleStride. https://www.pancan.org/get-involved/purplestride/.
18. ClinicalTrials.Org. https://clinicaltrials.gov/ct2/home.
19. National Cancer Research Institute. https://www.ncri.org.uk/trends-in-disease-site-spend/.
20. Recalcitrant Cancer Research Act. https://www.congress.gov/bill/112th-congress/house-bill/733.
21. NCI funding. https://www.cancer.gov/about-nci/budget/fact-book/data/research-funding.

Part III
The Pancreas

Chapter 11
Anatomy and Embryology of the Pancreatic Gland

Romana Urbas, Eckhard Klieser, Daniel Neureiter, and Erich Brenner

Take Home Messages

- The pancreas is a mainly exocrine, but also an endocrine gland.
- The pancreas is situated mainly retroperitoneally, except for the tail.
- The exocrine pancreas is set up of quite visible lobules, containing serous acini and intralobular ducts. It produces an alkaline juice rich in digestive enzymes, which is released into the duodenum via pancreatic ducts.
- The endocrine pancreas is composed of up to two million islets of Langerhans, distributed throughout the whole pancreas with a maximum in the tail. They produce insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin.

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Pearls and Pitfalls
- The pancreas is supplied by numerous vascular arcades from the coeliac trunk and the superior mesenteric artery.
- The complex development by a ventral and dorsal bud may result in several congenital anomalies of the pancreas.
- The pancreas is drained by a dense network of (initial) lymphatic vessels, except for the islet of LANGERHANS.

Future Perspectives
- Elaborating of the "real" prevalence of anatomical variations or variants. This would be especially interesting in the context of pathologies, such as acute pancreatitis.
- Based on the cascade of developmental activation of genes, detailed knowledge of their effect on pancreatic cancer stem cells will allow for emerging concepts and future perspectives.
- Gene expression analysis in patients with acute pancreatitis to discover outcome-controlling events.
- Detailed analysis of pancreatic stellate cells in the normal pancreas will allow for better interpretation of their transformation induced by tumour-secreted cytokines.

11.1 Introduction

The pancreas is an essential part of the gastrointestinal tract. Despite the prevailing opinion that everything about this organ has already been described (Box 11.1) [1], more recently the molecular genetic processes during human embryonic development are being uncovered, such as the role of the *HOX*-genes. It is increasingly recognized that these gene programs are also crucial for the development of several pancreas-related diseases, such as diabetes mellitus, obesity etc., and even for the development of pancreatic tumours [2, 3].

This chapter is intended to provide an overview of the accurate macroscopic and topographical anatomy and insights into the embryology available to date.

11.2 Basic Description of the Pancreas

The pancreas is 13–18 cm long and weighs about 70–90 g (range 40–120 g). The slightly tongue-shaped gland consists mainly of the serous exocrine gland with interspersed endocrine islets. It is situated secondary retroperitoneally, dorsal to the omental bursa. From its ventral aspect, the transverse mesocolon arises (Fig. 11.1).

The pancreatic gland projects approximately onto the first to second lumbar vertebrae and extends transversely from the duodenal C slightly ascending to the hilum

Box 11.1 Selected Historical Descriptions of the Pancreas and Its Functions [1]

300 BC—First description of the pancreatic gland by ***Herophilos of Chalcedon*** (325–255 BC) [4].

1642—Main pancreatic duct discovered by ***Johann Georg Wirsüng*** (1589–1643), a German physician who worked as a prosector in Padua [5]. The duct is also called WIRSUNG's duct.

1724—Accessory pancreatic duct dissected and delineated by ***Giovanni Domenico Santorini*** (1681–1737), an Italian anatomist [4]. The duct is also called SANTORINI's duct.

1833—Amylase, an enzyme also found in the exocrine pancreas, isolated from a malt solution by ***Anselme Payen*** (1795–1871), a French chemist [6].

1869—***Paul Langerhans*** (1847–1888) is awarded a doctorate for his thesis "On the more delicate structure of the pancreas" [7].

1893—Islets of LANGERHANS named in honour of ***Paul Langerhans*** (1847–1888) by ***Gustave-Edouard Laguesse*** (1861–1927), a French histopathologist [8].

1889—Lithuanian-German physiologist and pathologist ***Oskar Minkowski*** (1858–1931) and German physician ***Joseph von Mering*** (1841–1908) showed that removing the pancreas from a dog caused the animal to exhibit a disorder quite like human diabetes mellitus [9].

1921—Discovery of insulin by ***Frederick Banting*** (1891–1941) and ***Charles H. Best*** (1988–1978), two Canadian researchers [10]. In the same year purification of insulin with the help of Canadian chemist ***James B. Collip*** (1892–1965) and Scottish physiologist ***John Macleod*** (1876–1935) [11].

1923—Subsequently, Banting and Macleod won the 1923 Nobel Prize in Medicine. Banting shared his part of the prize money with Best, Macleod with Collip. Banting, Best and Collip subsequently shared the patent for insulin, which they symbolically sold to the University of Toronto for one dollar.

1953—Glucagon, called initially "hyperglycaemic glycogenolytic factor", purified by ***A. Staub***, ***L. Sinn*** and ***Otto K. Behrens*** [12].

of the spleen, behind the stomach. Macroscopically, four sections (head, neck, body, and tail) are distinguished (starting from right lateral to left lateral). From the inferior-dorsal portion of the head, the uncinate process arises to the left, forming—together with the neck—the pancreatic notch. Through this notch, the superior mesenteric vessels pass (Fig. 11.2).

The central functional part of the pancreas consists of serous exocrine glands, which produce 1.5–2.0 L alkaline juice daily with approximately 25 different digestive enzymes. The exocrine pancreatic secretion is released from the acinar units into multiple intercalated ducts, small intra- to larger interlobular ducts and finally into either the main or accessory pancreatic duct. The main pancreatic duct opens, together with the bile duct, at the major duodenal papilla into the descending part of the duodenum; the accessory pancreatic duct enters the duodenum a little more

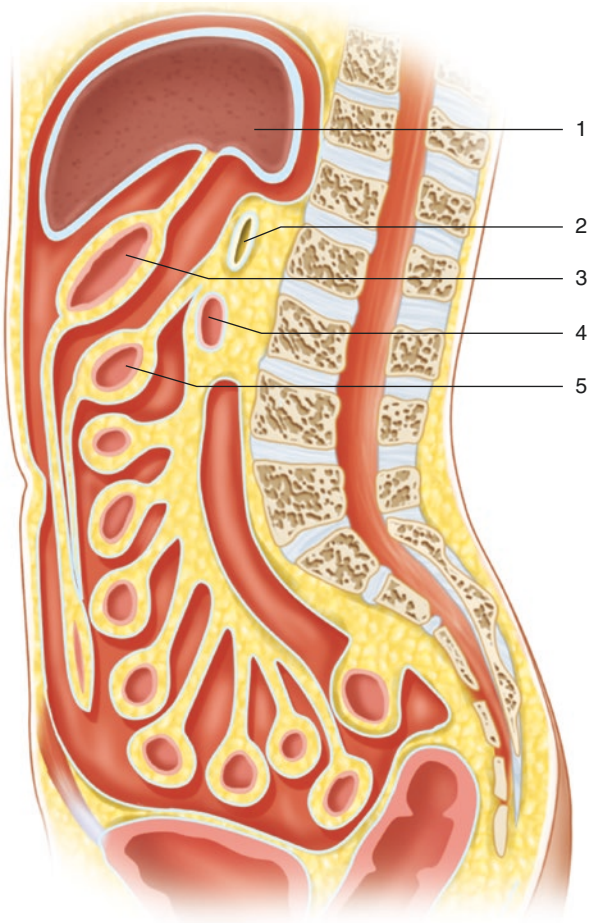

Fig. 11.1 The retroperitoneal position of the pancreas [13]. (1) Liver, (2) pancreas, (3) stomach, (4) horizontal part of the duodenum, (5) transverse colon. (Figure 6a from: 1. Hollender LF, Bahnini J. Chirurgische Anatomie des Pankreas. In: Hollender LF, Peiper HJ, editors. Pankreaschirurgie. Die Praxis der Chirurgie. Berlin, Heidelberg: Springer; 1988. p. 9–29)

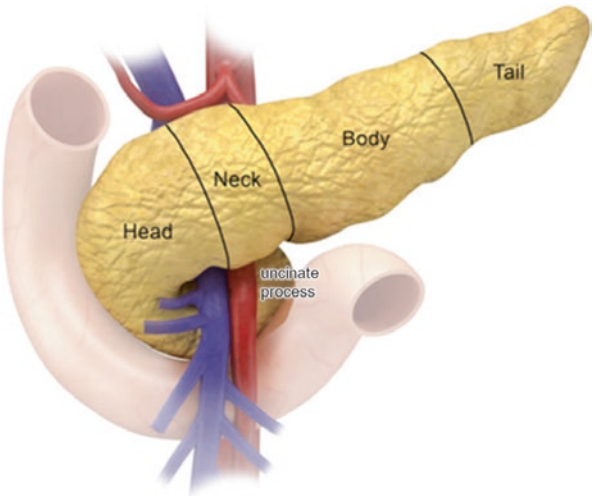

Fig. 11.2 Anatomical sections of the pancreas [14]. (Modified from figure 7.2 from: Chauhan A, Elsayes KM, Sagebiel T, Bhosale PR. The Pancreas. In: Elsayes KM, editor. Cross-Sectional Imaging of the Abdomen and Pelvis: A Practical Algorithmic Approach. New York, NY: Springer New York; 2015. p. 189–227)

orally at the minor duodenal papilla. At the periacinal regions, pancreatic stellate cells (PSCs) are localized, extending with long cytoplasmic projections towards the basolateral aspects of the acinar cells [15]. These cells also surround the perivascular and periductal regions.

The endocrine portion is arranged as 0.5–2.0 million islets (of LANGERHANS) with a diameter of 0.1–0.4 mm mainly located in the tail, less in the body or upper part of the head. These cells constitute up to only 1–2% of the entire volume of the gland. The primary function of this island-like aggregates is to regulate glucose metabolism. Sixty per cent of the endocrine cells (β cells) produce insulin, about 20% (α cells) glucagon, and the rest is equally distributed between δ cells (somatostatin), PP cells (pancreatic polypeptide), and ε cells (ghrelin). These hormones are fed into a capillary network surrounding the islets and are subsequently transported to the liver via the pancreatic veins and the portal vein.

11.3 Development of the Pancreas

Pancreatic development is based on several steps: (1) the formation of both a ventral and a dorsal evagination (bud) of the aboral foregut, (2) the rotation of the ventral bud around the foregut, (3) the fusion of these two buds to one single organ, and (4) endodermal growth by dichotomy branching (Fig. 11.3).

According to the classical Carnegie stages (Box 11.2) [16], in stage 13, the dorsal pancreatic bud arises at first as a thickening of the endodermal tube, which

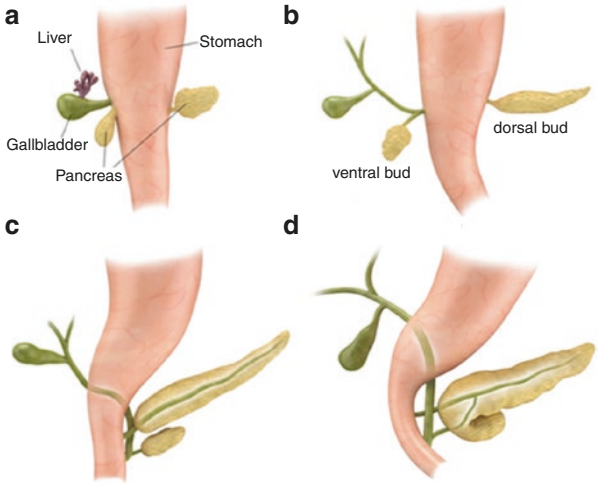

Fig. 11.3 Pancreatic embryology. The illustration shows progressive embryological development of pancreas as separate dorsal and ventral buds later fusing to form the pancreas. (**a**) Sprouting of the hepatic and both the ventral and dorsal pancreatic buds. (**b**) Fusion of the hepatic and the ventral pancreatic bud. (**c**) Rotation of the ventral pancreatic duct around the foregut. (**d**) Fusion of the ventral and the dorsal pancreatic buds. (Modified from figure 7.1 from: Chauhan A, Elsayes KM, Sagebiel T, Bhosale PR. The Pancreas. In: Elsayes KM, editor. Cross-Sectional Imaging of the Abdomen and Pelvis: A Practical Algorithmic Approach. New York, NY: Springer New York; 2015. p. 189–227)

Box 11.2 Human Pancreas Development in Carnegie Stages

Stage 13 (week 4–5, 28–32 days)—Formation of the pancreatic buds, with the larger dorsal bud at first.

Stage 14 (week 5, 31–35 days)—Formation of the pancreatic buds, with the smaller ventral bud later.

Stage 15 (week 5, 35–38 days)—Rotation of the ventral bud around the aboral foreguts.

Stage 16 (week 6, 37–42 days)—dorsal and ventral pancreatic buds are contiguous.

Stage 19 (week 7, 48–51 days)—differentiation in "trunk" and "tip" progenitor cells.

Stage 23 (week 8, 56–60 days)—Formation of foetal β cells and ductal cells.

Week 10—α cells differentiate first, then δ cells, and β cells; insulin secretion begins.

Week 15—glucagon secretion begins.

The embryonic period in the human is subdivided into 23 Carnegie stages, a term introduced by O'Rahilly. These stages are based on both external and internal morphological criteria [16].

proliferates into the dorsal mesogastrium [17]. In close, in stage 14, the ventral pancreatic bud appears as an evagination from the bile duct in the ventral mesogastrium [18]. It is generally described as unpaired but, at least in some cases, may perhaps be bilobed [19] or even multiple [20]. Both pancreatic buds were found within a few cells from the ventral and dorsal anastomoses of the left and right vitelline veins, which eventually form the portal vein, and contained micro-lumina [21]. As a result of differential growth of the duodenum, which rotates 90 degrees clockwise and becomes "C"-shaped, the right ventral pancreatic bud section comes to lie below and behind the dorsal pancreatic bud in stage 15. In that stage, the pancreas was widely separated from the aorta; however, gut rotation had brought both ventral and dorsal pancreatic buds to either side of the portal vein [21]. Until stage 17, both pancreatic buds have fused [18, 22], and perhaps the ventral and dorsal ducts have begun to blend [23]. At stage 19, differentiation in "trunk" and "tip" progenitor cells take place [21], with the "trunk" progenitors developing into foetal β cells and ductal cells (stage 23), and the "tip" progenitors into acinar cells (foetal period, week 14). In the foetal period, islet cell clusters differentiate from pancreatic bud endoderm: these cell clusters form (exocrine) acini and ducts. On the edge of these cell clusters also (endocrine) pancreatic islets form. The exocrine pancreas function begins after birth, while the endocrine function (hormone release) can be measured from weeks 10 to 15 onward. At week 10, α cells (glucagon) differentiate first, then δ cells (somatostatin), β cells (insulin) differentiate, and insulin secretion begins. In week 15, glucagon is detectable in foetal plasma. First, α-cells and β-cells are organized into a thick folded plate lined at both sides with vessels [24]. α-Cells are mostly at the periphery of the plate and in close contact with vessels. β-Cells occupy a more central part of the plate and most of them develop cytoplasmic extension that

runs between α-cells and reaches the surface of vessels [25]. The plate with adjacent vessels is folded so that it forms an islet.

The final position of the pancreas is determined by growth and rearrangement processes in the abdominal cavity. The stomach shifts with its rotation to the left and the duodenum corresponding to the right. This moves the dorsal mesogastrium and the dorsal mesoduodenum with the pancreas against the posterior abdominal wall where they fuse with the parietal peritoneum. The original intraperitoneally located pancreas is shifted into a secondary retroperitoneal position. Only its tail preserves in most cases an intraperitoneal position.

The right ventral pancreatic bud section forms the posterior part of the head and the posterior part of the uncinate process, whereas the rest of the pancreas is formed by the dorsal pancreatic bud (the anterior part of the head, the neck, the body, and the tail). The left ventral pancreatic bud atrophies typically, but when it persists and continues to grow, it surrounds the duodenum in a ring shape and connects to the pancreatic head. This results in an annular pancreas with consequent constriction of the duodenum and thereby duodenal stenosis (Fig. 11.4).

Fig. 11.4 Annular pancreas. Abnormal fusion of dorsal and ventral pancreatic buds encircling the descending part of the duodenum. (Figure 7.7 from: Chauhan A, Elsayes KM, Sagebiel T, Bhosale PR. The Pancreas. In: Elsayes KM, editor. Cross-Sectional Imaging of the Abdomen and Pelvis: A Practical Algorithmic Approach. New York, NY: Springer New York; 2015. p. 189–227)

Box 11.3 Congenital Anomalies of the Pancreas

- **Agenesis**: Prevalence: <1 in 1,000,000; Inheritance: autosomal recessive; aetiology: Caused by homozygous or compound heterozygous mutation in the *PDX1* gene (13q12.1), which encodes a transcription factor, insulin promoter factor 1 (IPF-1). Missense mutations in the *PTF1A* gene (10p12.3) were found to be the cause of the autosomal recessive syndrome of neonatal diabetes mellitus with cerebellar and/or pancreatic agenesis.
- **Pancreas divisum**: Persistence as dorsal and ventral pancreas. In autopsy series, a complete pancreas divisum can be detected in about 5–10% of cases.
- **Pancreas bifidum ("double-split pancreas")**: The main excretory duct in the tail of the pancreas is split like the tail of a fish. In everyday clinical practice, these are usually sporadic accidental findings.
- **Annular pancreas**: Prevalence: 1:250 [26] to 1:20,000 [27]. Pancreatic head encircles the duodenum with the risk of obstruction; persistence of two separate pancreatic ducts from dorsal and ventral pancreas predisposes to recurrent pancreatitis.
- **Ectopic (aberrant) pancreatic tissue**: The prevalence of ectopic pancreas in autopsy series is about 0.55–14% [28]. They are located in the stomach, duodenum, jejunum, Meckel diverticulum, ileum, and liver, where they appear as single or multiple yellow-grey nests (from several mm up to 3–4 cm in diameter) in the submucosal layer.

The main pancreatic duct (of Wirsung) is formed by the fusion of the distal part of the dorsal pancreatic duct and the entire ventral pancreatic duct and enters the duodenum combined with the bile duct at the major papilla (of Vater). Until the postnatal period, the proximal portion of the dorsal pancreatic duct either obliterates or persists as an accessory pancreatic duct (of Santorini), entering the duodenum at the minor papilla (10% adults), so-called pancreas divisum (Box 11.3 and Fig. 11.5).

11.4 Cellular Development of the Pancreas

Differentiation and early specification of pancreatic endoderm are induced by fibroblast growth factor 2 (FGF2) and activin (a Transforming growth factor-beta (TGF-β) family member), both produced by the notochord and endothelium of the dorsal aorta. Both repress the expression of the transcription factor Shh locally in the gut endoderm, destined to form the dorsal pancreatic bud. Endoderm lying caudally to the pancreatic region does not respond to those signals. The ventral bud is induced by upregulation of the pancreatic and duodenal homeobox 1 (PDX1) gene from the

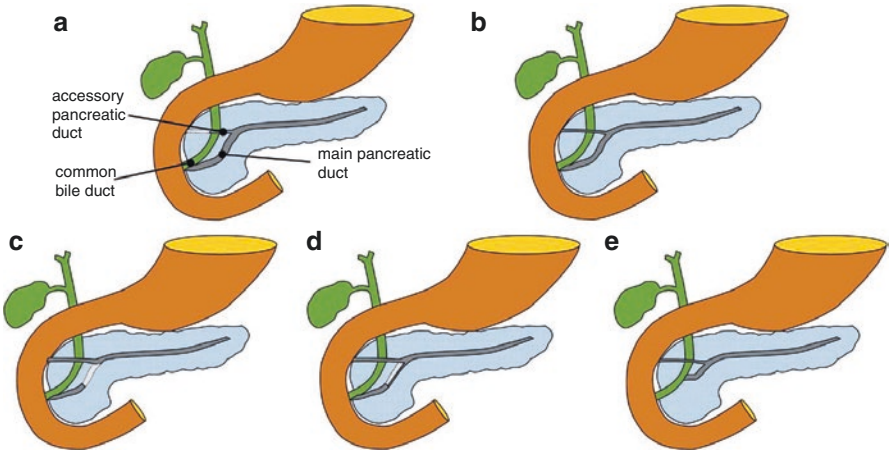

Fig. 11.5 Schematic representation of various fusion anomalies of the pancreas. (**a**) Regular duct anatomy; (**b**) standard variant; (**c**) pancreas divisum; (**d**) incomplete pancreas divisum; (**e**) "long common channel". (Modified from figure 21.3 from: Witt H. Physiologie und Embryologie des Pankreas. In: Rodeck B, Zimmer K-P, editors. Pädiatrische Gastroenterologie, Hepatologie und Ernährung. Berlin, Heidelberg: Springer; 2008. p. 451–7)

splanchnic mesoderm. Several anomalies may develop (Box 11.3) due to faulty cellular development of embryogenesis of the gland.

From 10th to 15th week, the primitive endodermal ductal epithelium provides the stem cell population for all the secretory cells, which are initially located in the duct walls or in the buds, from which they arise. Islet differentiation proceeds in two phases: Phase I (9th–15th week) is characterized by the proliferation of polyhormonal cells, whereas the differentiation of mono-hormonal cells is seen from week 16 onwards, referred to as phase II. Later, these endocrine cells accumulate in pancreatic islets (of LANGERHANS) and scatter throughout the pancreas, starting with insulin and amylin secretion by β-cells approximately at the fifth month until the neonatal period. The dorsal bud gives rise mostly to α-cells, which produce glucagon; however, most of the pancreatic polypeptide producing γ-cells develop from the ventral bud. After week 30, somatostatin-producing δ-cells are seen. The remaining primitive duct cells will either differentiate into definitive duct cells with microvilli and cilia or into acinar cells in which zymogen granules or acinar cell markers can be detected at week 12–16.

Correct ductal branching pattern and formation of acinar structures are determined by pancreatic mesenchyme which gives rise to the connective tissue between the ducts resulting in pancreatic proliferation and maintaining the relative proportions of acinar, α- and β-cells. Additionally, it provides cell lines for smooth muscle within the pancreatic tissue, and angiogenic mesenchyme produces blood and lymphatic vessels.

11.5 Macroscopy and Topography

The head of the pancreas (4–8 cm wide, 2–3 cm thick) lies in the concavity of the duodenal loop (descending duodenum) and merges dorsally into a hook-shaped extension (uncinate process), which here includes the superior mesenteric vessels. These vessels are initially located at the posterior wall of the pancreas and emerge ventrally in the pancreatic notch, which marks the transition between the head and body. This approximate 2 cm wide parenchymal strip ventral to the superior mesenteric vessels is often called the pancreatic neck for surgical-practical reasons. At the caudal end of the head, the horizontal part of the duodenum is located. The pancreatic head is flat in cross-section, so that only an and a posterior surface—delimited by a superior and inferior margin, respectively—can be distinguished.

The pancreatic body (2–3 cm wide, 1.5–2.5 cm thick) begins at the pancreatic notch, crosses at the level of the first or second lumbar vertebra, whereas it protrudes as omental eminence of pancreas towards the omental bursa, the spinal column as well as the abdominal aorta, and continues without a sharp border into the pancreatic tail.

The pancreatic body is triangular in cross-section and shows three surfaces: a posterior surface, which is bordered cranially by the superior margin and caudally by the inferior margin; an anterior surface, which is itself divided by the anterior margin into a larger anterosuperior surface and a smaller anteroinferior surface. The anterosuperior surface is covered by secondary peritoneum and forms most of the posterior wall of the omental bursa. Here along the anterior margin, at the head and tail the inferior margin, the mesocolic root is attached, which forms a duplication of the peritoneum with the posteroinferior layer of the transverse mesocolon. The two layers of the transverse mesocolon diverge along this border. One passes up over the anterosuperior surface while the other runs downwards and backwards over the anteroinferior surface (Fig. 11.6).

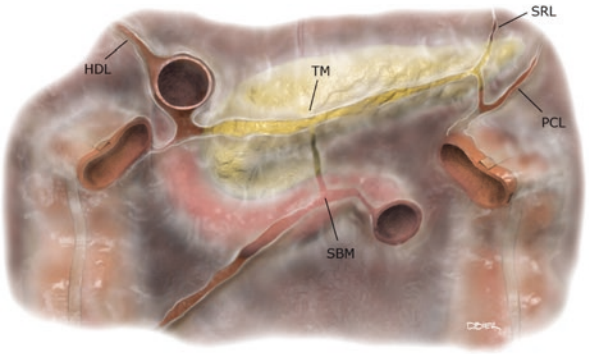

Fig. 11.6 Frontal representation of the peritoneal ligaments and their relationships to the pancreas. *HDL* hepatoduodenal ligament, *PCL* phrenicocolic ligament, *SBM* small bowel mesentery, *SRL* splenorenal ligament, *TM* transverse mesocolon. (Figure 2 from: 1. Vikram R, Balachandran A, Bhosale PR, Tamm EP, Marcal LP, Charnsangavej C. Pancreas: peritoneal reflections, ligamentous connections, and pathways of disease spread. Radiographics. 2009;29(2):e34. https://doi.org/10.1148/rg.e34)

The pancreatic tail (2 cm wide, 1–2 cm thick) is oval flattened in cross-section. A superior and inferior margin again limits anterior and posterior surfaces. The most lateral portion of the gland lies between the layers of the splenorenal ligament and is sometimes bifid. It may end up at the base of the splenorenal ligament or extend up nearly as far as or contact the splenic hilum as well as splenic vessels and its tributaries.

The main excretory duct of the pancreas of WIRSUNG has a diameter of about 2–5 mm and runs longitudinally through the gland close to the posterior surface. It collects numerous small side branches and in 60% of cases merges with the final section of the (common) bile duct to form the hepatopancreatic ampulla, which enters the descending duodenum at the major duodenal papilla (tubercle of VATER). In 65% of the cases, there is an additional accessory pancreatic duct (duct of SANTORINI), which drains the lower parts of the head and the uncinate process and opens separately on the minor duodenal papilla located about 2 cm orally to the major duodenal papilla.

11.6 Vascular Supply and Lymphatic Drainage of the Pancreas

The arterial supply of the pancreas (exo- and endocrine portion) is highly variable but follows a general pattern. The head of the pancreas is supplied by anastomosing branches from the celiac trunk and the superior mesenteric artery. These arteries form arcades in front and behind along the vertical axis: the superior pancreaticoduodenal artery (from the gastroduodenal artery) divides into a superior anterior branch anastomosing with the anterior branch of the inferior pancreaticoduodenal artery, and a superior posterior branch anastomosing with the posterior branch of the inferior pancreaticoduodenal artery, which arises from the superior mesenteric artery. The anterior and posterior arcades of the pancreatic head vary not only in number but also in origin (Fig. 11.7).

Head and neck are supplied by pancreatic branches of the splenic artery, the dorsal pancreatic and the inferior pancreatic artery. The dorsal pancreatic artery originates splenic artery or the coeliac trunk directly and enters the parenchyma at the pancreatic neck. This artery anastomoses by a transverse branch with the posterior superior pancreaticoduodenal artery, continues to the lower edge of the gland, and anastomoses with the inferior pancreatic artery to supply the tail. If that transverse branch is sturdy, it is called the great pancreatic artery, which runs transversely from the middle of the body to the tail. The tail additionally receives blood from an artery to tail of pancreas originating near the splenic hilum.

The terminal arteries entering the lobules of the gland branch out to form arterioles and further to capillary balls, initially to the endocrine and then to the exocrine parts. The efferent capillaries emerging from the endocrine islets open into the capillary system, which surrounds the exocrine acini. This is referred to as the “portal system of the pancreas”. Thereby the hormones released by the islets released into the capillary plexus around the endocrine islets can act immediately on the exocrine glandular lobes. For example, the hormones of the PP cells (pancreatic polypeptide and adrenomedullin) inhibit the exocrine gland cells.

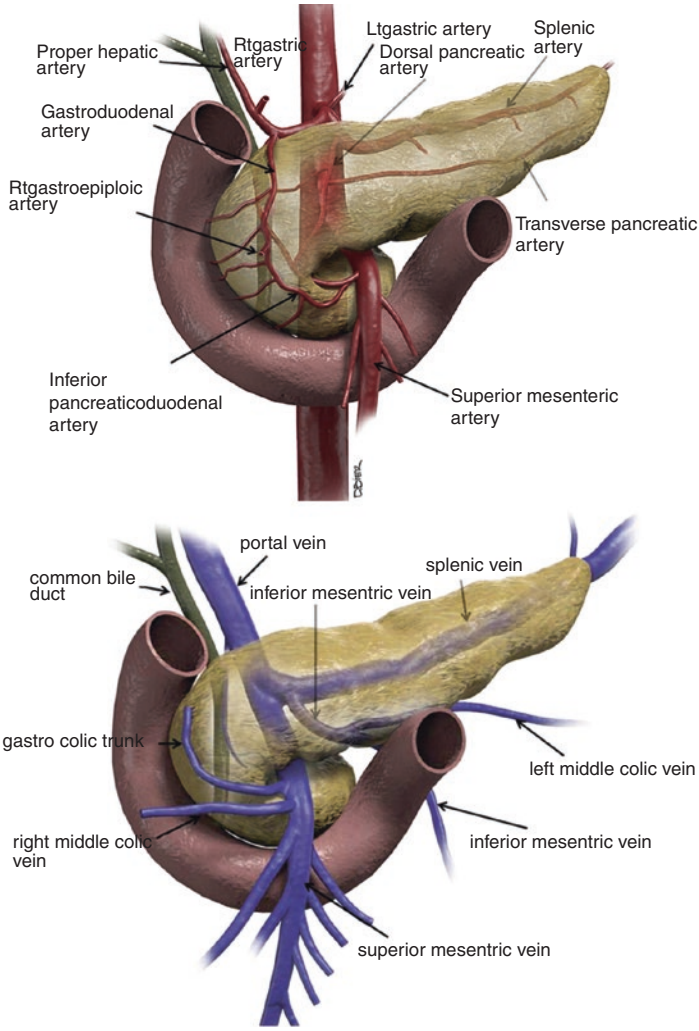

Fig. 11.7 Vascular supply of the pancreas. *Lt* left, *Rt* right. (Figures 3 and 4 from: Vikram R, Balachandran A, Bhosale PR, Tamm EP, Marcal LP, Charnsangavej C. Pancreas: peritoneal reflections, ligamentous connections, and pathways of disease spread. Radiographics. 2009;29(2):e34. https://doi.org/10.1148/rg.e34)

The venous drainage of the pancreas is mainly into the portal system. The head and uncinated process drain primarily to the superior and inferior pancreaticoduodenal veins. The body and tail drain mostly by small veins directly into the splenic vein along the posterior part of the gland; occasionally they can drain into the portal vein directly. Small venous vessels and venules exist between the pancreas and retroperitoneal veins (veins of RETZIUS), draining into the lumbar veins, which may expand in case of portal hypertension.

Initial lymphatic vessels commence around the capillary system of the exocrine acini. Most vessels forming this network lie in the interlobular septa of connective tissue that subdivide the pancreas into lobes and lobules [29]. Peripheral extensions of these interlobular lymphatics can be found within the lobules, but these intralobular lymphatics are relatively sparse. Rarely are there lymphatics associated with islets of LANGERHANS, and then only where lymphatic vessels in connective tissue septa pass close to a pancreatic lobule that contains an islet at its periphery [30]. The larger lymphatic vessels follow the arterial supply. The lymphatics of tail and body drain mostly into the (pancreatico)-splenic nodes, some drain directly to pre-aortic nodes. Additionally, the tail drains into splenic, mesocolic and cardiac nodes and the body to lumbar nodes. From the superior part of the head and neck lymphatics drain more widely via anterior and posterior pancreaticoduodenal nodes to the hepatic lymph nodes. In contrast, drainage from the inferior part of the head and neck goes directly into superior mesenteric lymph nodes.

Development of lymphatics around the pancreas starts at week 9 when the first LYVE1- and PDPN-expressing lymphatic vessels appear [31]. The blood and lymphatic machinery in the human pancreas are in place to support endocrine function from weeks 17–22 onwards.

11.7 Innervation of the Pancreas

The pancreas is innervated by a delicate network of sympathetic and parasympathetic fibres. The sympathetic supply originates from the sixth to tenth thoracic spinal segments and is mainly distributed via the sympathetic contribution to the coeliac ganglia. Postganglionic fibres are distributed to the gland as periarterial plexuses along the arteries. The parasympathetic supply comes from the posterior vagus nerve (partly from the stomach branches) and the parasympathetic component of the coeliac plexus. The supply to the gland is both: vasomotor (sympathetic) and parenchymal (sympathetic and parasympathetic) in distribution. The exocrine lobules are innervated by fine sympathetic and parasympathetic fibres. Sensory fibres from the lobules run in both the sympathetic and parasympathetic system (Fig. 11.8).

Delicate parasympathetic fibres among the cells within the endocrine islets and form plexuses around the islets. Fibres frequently synapse with acinar cells of the exocrine part of the gland before innervating the islets, suggesting a close linkage between neural control of exo- and endocrine components. Fibres enter the islets along with the arterioles, and parasympathetic ganglia lie in the connective tissue within and between the lobules forming neuro-insular complexes. This neuro-insular complex influences each other, so acetylcholine in the presence of glucose can increase the secretion of insulin. Noradrenaline, on the other hand, inhibits the secretion of insulin. Galanin in the noradrenergic fibres stimulates glucagon secretion and inhibits insulin secretion.

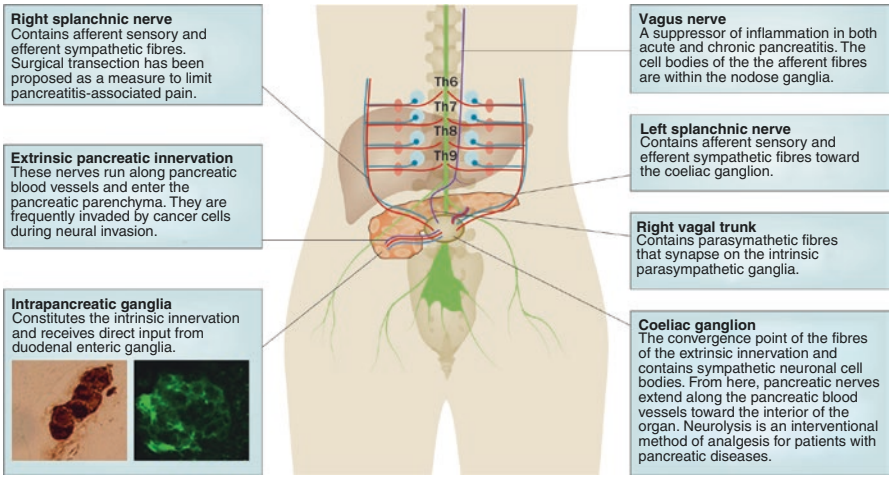

Fig. 11.8 Anatomy of pancreatic innervation. The pancreas possesses extrinsic and intrinsic innervation. Extrinsic innervation stems from the vagus nerve and splanchnic nerves, which convey sensory nerve fibres from the dorsal root ganglia and sympathetic nerve fibres from the ganglia of the sympathetic chain. Upon their convergence on the coeliac trunk, extrinsic fibres enter the pancreas along major pancreatic blood vessels. Fibres of the vagus nerve can either directly enter the pancreas or run partially through the coeliac trunk to finally synapse on the intra-organ intrinsic ganglia. Intrinsic innervation is composed of intrapancreatic ganglia that are frequently located on LANGERHANS islets. (Figure 1 from: Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. Nature Reviews Gastroenterology & Hepatology. 2015;12(11):649–59. https://doi.org/10.1038/nrgastro.2015.166)

11.8 Conclusion

As in many organs, the main morphological features of the pancreas are well known: the pancreas is both an exocrine and an endocrine gland at the dorsal wall of the upper abdomen. Its alkaline juice rich in digestive enzymes is released into the duodenum. Its hormones released to the pancreatic portal system act both locally on the pancreatic acini and the whole body. The interrelation of maternal diabetes mellitus and the development of especially α-cells indicate that not only the embryo's genes but also the maternal hormones influence the development and growth of the pancreas.

References

1. Hollender LF. Geschichte des Pankreas—allgemeine Betrachtungen. In: Hollender LF, Peiper H-J, editors. Pankreaschirurgie. Die Praxis der Chirurgie. Berlin: Springer; 1988. p. 1–7.
2. Gray S, Pandha HS, Michael A, Middleton G, Morgan R. *HOX* genes in pancreatic development and cancer. JOP. 2011;12(3):216–9.

3. Kuo TL, Cheng KH, Chen LT, Hung WC. Deciphering the potential role of Hox genes in pancreatic cancer. Cancers (Basel). 2019;11(5):734. https://doi.org/10.3390/cancers11050734.
4. Howard JM, Hess W. The early surgeon-anatomists. In: History of the pancreas: mysteries of a hidden organ. Boston, MA: Springer; 2002. p. 1–64.
5. Howard JM, Hess W, Traverso W. Johann Georg Wirsüng (1589-1643) and the pancreatic duct: the prosector of Padua, Italy. J Am Coll Surg. 1998;187(2):201–11. https://doi.org/10.1016/s1072-7515(98)00136-7.
6. Payen A, Persoz J-F. Mémoire sur la diastase, les principaux produits de ses réactions, et leurs applications aux arts industriels. Ann Chim Phys. 1833;53:73–92.
7. Langerhans P. Über den feineren Bau der Bauchspeicheldrüse. Institut für Pathologie. Berlin: Universität Berlin; 1869.
8. Laguesse M. Sur la formation des ilots de Langerhans dans le pancreas. C R Seances Soc Biol. 1895;47:699–701.
9. von Mering J, Minkowski O. Diabetes mellitus nach Pankreasexstirpation. Archiv für experimentelle Pathologie und Pharmakologie. 1890;26(5–6):371–87.
10. Banting FG, Best CH. The internal secretion of the pancreas. J Lab Clin Med. 1922;7(5):251–66.
11. Banting FG, Best C, Collip J, Macleod J. The preparation of pancreatic extracts containing insulin. Trans R Soc Can. 1922;16:27–9.
12. Staub A, Sinn L, Behrens OK. Purification and crystallization of hyperglycemic glycogenolytic factor (HGF). Science. 1953;117(3049):628–9. https://doi.org/10.1126/science.117.3049.628.
13. Hollender LF, Bahnini J. Chirurgische Anatomie des Pankreas. In: Hollender LF, Peiper HJ, editors. Pankreaschirurgie. Die Praxis der Chirurgie. Berlin: Springer; 1988. p. 9–29.
14. Chauhan A, Elsayes KM, Sagebiel T, Bhosale PR. The pancreas. In: Elsayes KM, editor. Cross-sectional imaging of the abdomen and pelvis: a practical algorithmic approach. New York: Springer; 2015. p. 189–227.
15. Bynigeri RR, Jakkampudi A, Jangala R, Subramanyam C, Sasikala M, Rao GV, et al. Pancreatic stellate cell: Pandora's box for pancreatic disease biology. World J Gastroenterol. 2017;23(3):382–405. https://doi.org/10.3748/wjg.v23.i3.382.
16. O'Rahilly R, Müller F. Developmental stages in human embryos. Washington, DC: Carnegie Institution of Washington; 1987.
17. Politzer G. Zur Abgrenzung des Anlagebegriffes, erörtert an der Frühentwicklung von Parathyroidea, Pancreas und Thyroidea. Acta Anat (Basel). 1952;15(1–2):68–84. https://doi.org/10.1159/000140737.
18. Blechschmidt E, Kircheiss W. Die pränatalen Organsysteme des Menschen: untersucht unter funktionellen Gesichtspunkten. Stuttgart: Hippokrates-Verlag; 1973.
19. Odgers PN. Some observations on the development of the ventral pancreas in man. J Anat. 1930;65(Pt 1):1–7.
20. Delmas A. Les chauches pancreatiques dorsales et ventrales. Leurs rapports dans la constitution du pancreas definitif. Ann Anat Pathol. 1939;16:253–66.
21. Jennings RE, Berry AA, Kirkwood-Wilson R, Roberts NA, Hearn T, Salisbury RJ, et al. Development of the human pancreas from foregut to endocrine commitment. Diabetes. 2013;62(10):3514–22. https://doi.org/10.2337/db12-1479.
22. Streeter GL. Developmental horizons in human embryos. Description of age groups XV, XVI, XVII, XVII, being the third issue of a survey of the Carnegie collection. Contr Embryol Carnegie Instn Wash Publ. 1948;32:133–203.
23. Russu I, Vaida A. Neue Befunde zur Entwicklung der Bauchspeicheldrüse. Acta Anat (Basel). 1959;38(1–2):114–25. https://doi.org/10.1159/000141491.
24. Bosco D, Armanet M, Morel P, Niclauss N, Sgroi A, Muller YD, et al. Unique arrangement of alpha- and beta-cells in human islets of Langerhans. Diabetes. 2010;59(5):1202–10. https://doi.org/10.2337/db09-1177.
25. Hill MA. Endocrine—pancreas development. 2020. https://embryology.med.unsw.edu.au/embryology/index.php/Endocrine_-_Pancreas_Development. Accessed 14 May 2020.

26. Baggott BB, Long WB. Annular pancreas as a cause of extrahepatic biliary obstruction. Am J Gastroenterol. 1991;86(2):224–6.
27. Ravitch MM, Woods AC Jr. Annular pancreas. Ann Surg. 1950;132(6):1116–27. https://doi.org/10.1097/00000658-195012000-00011.
28. Cho JS, Shin KS, Kwon ST, Kim JW, Song CJ, Noh SM, et al. Heterotopic pancreas in the stomach: CT findings. Radiology. 2000;217(1):139–44. https://doi.org/10.1148/radiology.217.1.r00oc09139.
29. O'Morchoe CC. Lymphatic system of the pancreas. Microsc Res Tech. 1997;37(5–6):456–77. https://doi.org/10.1002/(SICI)1097-0029(19970601)37:5/6<456::AID-JEMT9>3.0.CO;2-B.
30. Korsgren E, Korsgren O. An apparent deficiency of lymphatic capillaries in the islets of Langerhans in the human pancreas. Diabetes. 2016;65(4):1004–8. https://doi.org/10.2337/db15-1285.
31. Roost MS, van Iperen L, de Melo Bernardo A, Mummery CL, Carlotti F, de Koning EJ, et al. Lymphangiogenesis and angiogenesis during human fetal pancreas development. Vasc Cell. 2014;6(1):22. https://doi.org/10.1186/2045-824X-6-22.

Chapter 12
Vascular Supply: Important Arterial and Venous Variants

P. Szatmary and Declan F. J. Dunne

Take Home Messages

- The pancreas derives its arterial blood supply from the gastroduodenal (head), splenic (body/tail) and superior mesenteric (uncinate process) arteries. There are multiple intra-pancreatic anastomoses.
- Variations of hepatic arterial anatomy are common but can usually be identified on pre-operative imaging.
- Portal venous anatomy has very little variation, permitting safe tunnelling under the neck of the pancreas.

Pearls and Pitfalls

- A fully replaced or accessory right hepatic artery will run postero-laterally to the portal vein, and postero-medially to the bile duct, in the hepatic ligament. Beware the risk of injury of this vessel during bile duct transection in pancreatoduodenectomy.
- Hepatic arterial flow may be reliant on flow through the gastro-duodenal artery. Consider this possibility before its transection in pancreatoduodenectomy.

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12.1 Introduction

Surgical resection of the pancreas remains the only chance for cure for patients with pancreas cancer and may be necessary for other neoplasms such as pancreatic neuroendocrine tumours or, in select cases, isolated metastases to the pancreas [1–3]. Resection of the whole pancreas is feasible but associated with significant short- and long-term morbidity (presented in another chapter of this book) [4]. Resection of part of the pancreas helps retain some exocrine and endocrine function but is only possible due to its dense network of collateral blood supply which ensure a well vascularised pancreatic remnant and permit healing of the pancreatic anastomosis.

The human pancreas develops at the interface of the embryological foregut and midgut in parallel with the blood supply to these structures [5]. It is derived predominantly from cells from the caudal foregut [6] and derives the majority of its blood supply from the foregut artery—the coeliac axis (CA). Owing to its proximity to the midgut, however, it has multiple anastomoses with the artery of the midgut—the superior mesenteric artery (SMA)—which abuts the head and uncinate process in the adult. Knowledge of the multiple anastomoses between these two arterial systems around the pancreas and their multiple variants are essential when planning and performing pancreatic resections. Hence, high quality preoperative imaging is of utmost importance as it gives specialist surgeons the opportunity to visualise any variation before encountering it during resection. The following chapter describes the development of the commonest arterial configurations of the pancreatic blood supply, frequent variants and relevance to surgical resection.

12.2 Arterial Supply: Development of Normal and Variant Anatomy

The development of the pancreas is described in detail in a previous chapter and helps to explain both normal and variant anatomy of its blood supply. The posterior pancreatic bud develops within the dorsal mesentery of the foregut along with the spleen and shares its blood supply (Fig. 12.1). It becomes the body and tail of the pancreas in the adult. The ventral foregut endoderm gives rise to the ventral pancreatic bud as well as structures that develop into the liver, bile ducts and gallbladder [7] at the junction with the midgut. These structures share their blood supply in the ventral mesentery of the foregut, derived from individual vitelline arteries which communicate in a ventral anastomotic artery [8].

Rapid growth of the duodenum pushes the duodenum off the midline and to the right, which together with a clockwise rotation of the stomach causes the ventral pancreatic bud to rotate behind the duodenum and portal vein, trapping the mesenteric vessels between the two buds. The ventral bud fuses with the dorsal pancreas to become the pancreatic head and uncinate process. In this way, the common configuration of the pancreatic head and uncinate process receiving its primary blood supply from the common hepatic artery via the gastro-duodenal artery as well as the

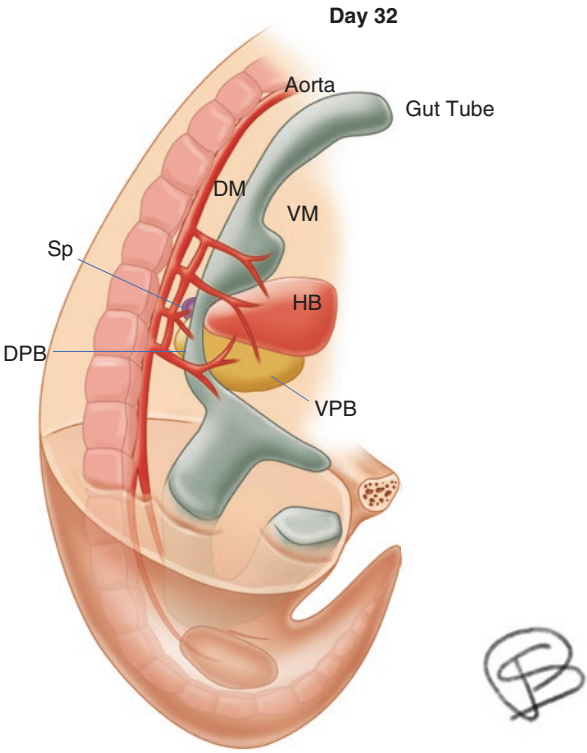


Fig. 12.1 Sketch of day 32 human embryo in sagittal section through thorax and abdomen. *HB* hepatic bud, *VPB* ventral pancreatic bud, *DPB* dorsal pancreatic bud, *Sp* spleen, *DM* dorsal mesentery, *VM* ventral mesentery

superior mesenteric artery, and the body and tail receiving its supply from the splenic artery is established.

The embryonic liver develops from three distinct lobes, each with their own arterial blood supply [9]. Failure of the embryological right and left hepatic arteries to regress is relatively common, around 5% in cadaveric studies and up to 20% in angiographic studies [8], and results in their persistence as replaced (or accessory if only supplying part of a hepatic segment) right or left hepatic arteries arising from the SMA or left gastric artery (LGA) respectively (Fig. 12.2). While a replaced left hepatic artery is of limited clinical relevance with regard to pancreatic surgery, a replaced right hepatic artery typically runs postero-lateral to the common bile duct and is prone to injury during portal dissection and division of the bile duct when performing a pancreatoduodenectomy.

12.3 Venous Supply: Development of Normal and Variant Anatomy

The liver is the main haematopoetic organ of the developing foetus and is also the interface between foetal and maternal circulation. The hepatic venous anatomy undergoes extensive remodelling throughout development. Of particular relevance

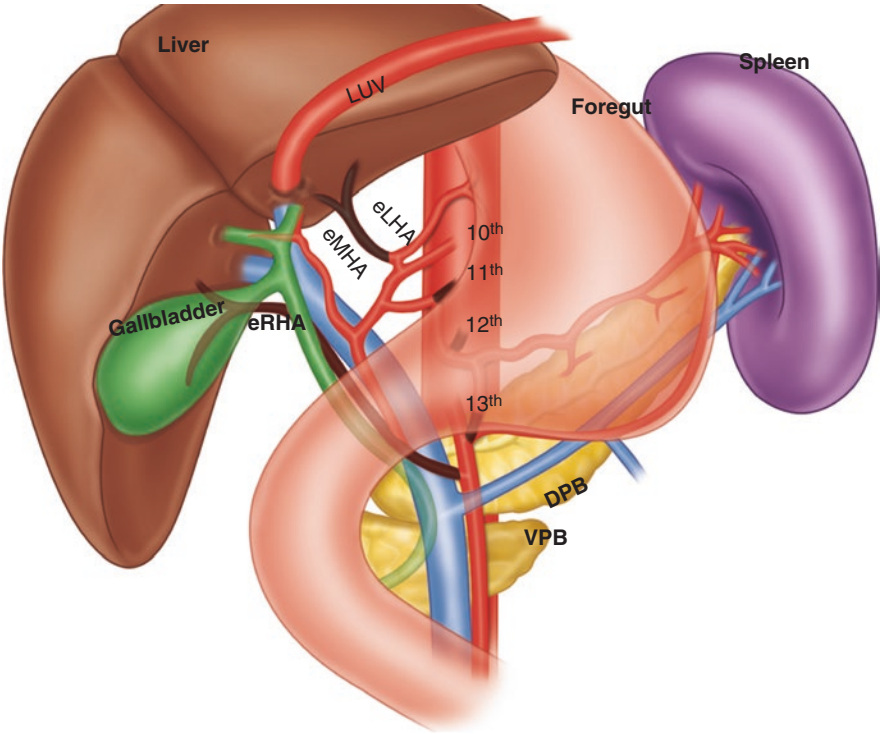


Fig. 12.2 Sketch of embryonic upper abdominal vasculature. *VPB* ventral pancreatic bud, *DPB* dorsal pancreatic bud, *LUV* left umbilical vein, *eLHA* embryonic left hepatic artery, *eMHA* embryonic middle hepatic artery, *eRHA* embryonic right hepatic artery, *10–13th* 10–13th anterior vitelline arteries. Vessels filled in black regress during embryonic development

to pancreas surgery, however, is the development of the portal vein. The portal vein develops from two parallel vitelline veins coursing alongside the gut tube, from the controlled regression of its caudal, ventral anastomosis [10–12] resulting in its standard anatomical course running behind the first part of the duodenum (Fig. 12.3). A pre-duodenal course of the portal vein is very rare and often part of other congenital malformations such as syndromic biliary atresia [13]. It is of interest to the liver surgeon, as patients frequently require transplantation early in life, but no cases of pancreatic resection have been reported with this anomaly.

There is little research into the development of the intestinal portal venous system, however a recent study from Japan supports the notion that the superior mesenteric vein (SMV) develops from tissue folds/clefts derived from and adjacent to the SMA as opposed to regression of vitelline veins [14]. Development in this way may explain veins running together with their respective arteries and likely represent a different origin to solitary veins of the portal system such as the splenic or inferior mesenteric veins.

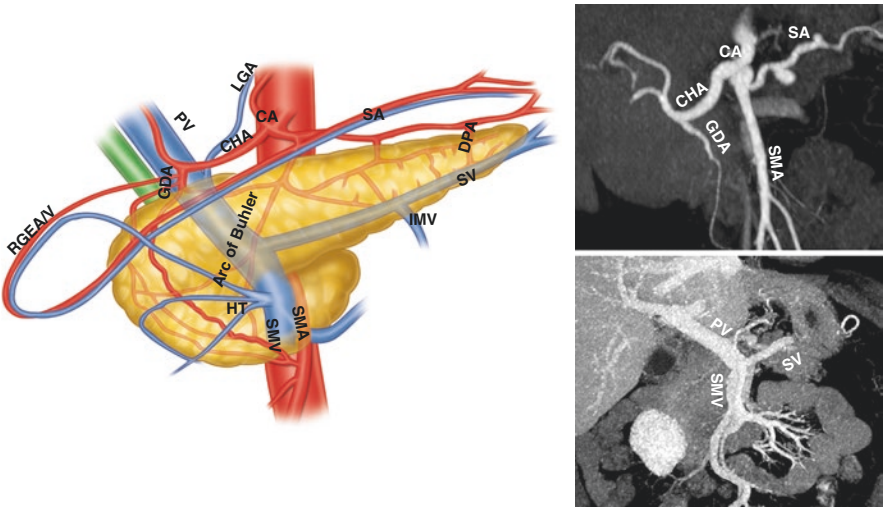


Fig. 12.3 Sketch of pancreas in the context of its blood supply, adjacent to contrast enhanced computerised tomography image in arterial and portal venous phase. *CA* coeliac axis, *LGA* left gastric artery, *SA* splenic artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *RGEA/V* right gastroepiploic artery and vein, *DPA* dorsal pancreatic artery, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *IMV* inferior mesenteric vein, *PV* portal vein, *HT* Henle's trunk

12.4 Pancreatoduodenectomy: Standard Anatomy

The distinct arterial supply to the pancreatic head and body permits partial resection of either part without compromising the blood supply to the remaining organ. While there is an extensive network of anastomoses, there is a relative paucity of major arteries at the site of the anatomical neck of the pancreas (Fig. 12.3), which has been demonstrated repeatedly in both radiological and cadaveric studies [15] and which makes this an ideal site for transection.

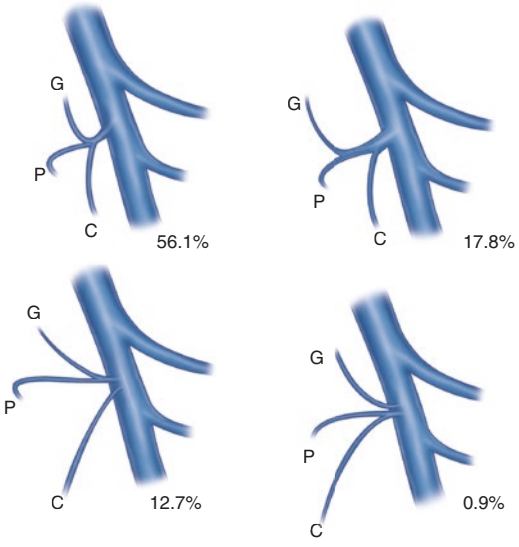
In order to resect the pancreatic head and duodenum, two arteries need to be divided: the gastroduodenal artery (GDA) and the inferior pancreaticoduodenal artery. This stops any arterial inflow to the pancreatic head with the exception of intra-pancreatic vascular anastomoses via the transverse pancreatic and/or dorsal pancreatic arcades. The GDA is relatively constant and divides first into the right gastroepiploic artery and then into the posterior superior pancreaticoduodenal artery. This vessel encircles the lower common bile duct and gives off choledochal branches as well as anastomotic branches to the anterior superior pancreaticoduodenal artery in the form of the middle pancreatic or Evrard's arcade [16]. The inferior pancreaticoduodenal artery is a common trunk arising off the SMA that divides into an anterior and posterior branch which anastomose with their superior pancreatic counterparts to form the vertical arcades of the pancreas [17]. This has been reported with a frequency of between 70 and 100% in the literature.

12.5 Pancreatoduodenectomy: Impact of Venous Drainage

The common venous drainage of the pancreas is also described in Fig. 12.3. Of particular relevance to the surgeon are the superior mesenteric vein, the pancreaticoduodenal venous arcades and the gastro-colic trunk of Henle.

The SMV runs slightly anterior and to the right of the SMA, and is made up from the confluence of a jejunal and ileal first order branch [18]. The jejunal branch passes behind the SMA in around 90% of cases [19], where it receives drainage from small veins of the uncinate process which need to be divided for pancreatic head resections. Where the jejunal branch passes anterior to the SMA, the uncinate veins usually drain into the ileal branch and are more accessible during surgery [18]. The jejunal branch is usually smaller than the ileal branch and can be ligated during pancreatoduodenectomy if involved with tumour.

The pancreaticoduodenal venous arcades consist of the superior- and inferior-pancreaticoduodenal veins, each with an anterior and posterior subdivision. The posterior superior pancreaticoduodenal vein drains into the right side of the supra-pancreatic portal vein behind the duodenum. It anastomoses with the posterior inferior pancreaticoduodenal vein to drain, either separately or together with the anterior inferior pancreaticoduodenal vein as a common trunk, passing behind the SMV into the first jejunal branch [20]. The anterior superior pancreaticoduodenal vein on the other hand drains anteriorly into the SMV at the inferior border of the pancreas, either directly or via the trunk of Henle. Although Henle originally described this trunk as the confluence of the right gastroepiploic vein and the right colic vein, this configuration occurs only in about 20% of cases [21]. The commonest configuration (>50%) is a confluence of the right gastroepiploic vein, the anterior superior pancreaticoduodenal vein and either the superior right- or right colic vein (Fig. 12.4). It is



Pancreatic Tributary	Pooled Prevalence
Anterior superior pancreaticoduodenal vein.	88.3%
Anterior inferior pancreaticoduodenal vein.	11.7%
Colic Tributary	
Superior right colic vein	82.5%
Right colic vein	24.1%
Middle colic vein	12.7%
Other	7.4%

Fig. 12.4 Sketch of trunk of Henle with frequency of its tributaries. *G* gastric tributary (always right gastroepiploic vein), *P* pancreatic tributary (see table), *C* colic tributary (see table)

of interest during pancreas head resection, as there are no other anterior branches of the SMV and portal vein caudal to the trunk, thereby making retro-pancreatic tunnelling possible. These vessels are also often very friable and liable to tearing from differential traction from an eager assistant, especially when retracting the transverse mesocolon downwards while the stomach is retracted superiorly. Ligation of Henle's trunk at its confluence with the SMV permits access to the SMV and portal vein facilitating resection, but will still necessitate further ligation of either the gastric or colic tributary in the majority of cases to avoid traction injury.

12.6 Pancreatoduodenectomy: Variant Anatomy

A number of variations exist to the above described anatomical configuration, some with critical relevance to pancreatic resection. One of the commonest and most significant is the replaced or accessory right hepatic artery (see above), which can be present in up to 20% of cases and is at risk of injury when dissecting the supra-pancreatic portal vein and when transecting the bile duct [22]. A dominant replaced right hepatic artery (present in around 7–10%; Fig. 12.5), or the rare variation—a fully replaced common hepatic artery arising from the SMA (present in around 1–2%) does, however, permit extended dissection around the coeliac axis, thus potentially allowing resection of locally advanced lesions without risking ischaemic

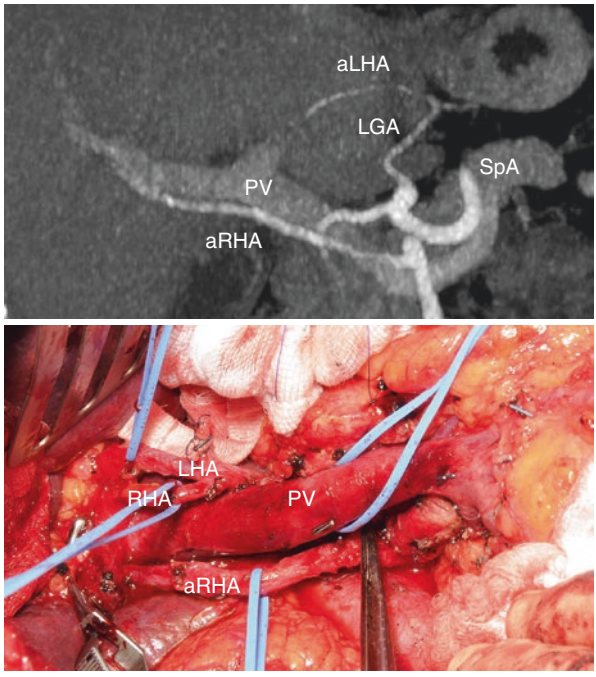


Fig. 12.5 Contrast enhanced computerised tomography image in arterial phase with corresponding intra-operative photograph of vascular anatomy in porta hepatis. *PV* portal vein, *RHA* right hepatic artery, *LHA* left hepatic artery, *aRHA* accessory right hepatic artery, *aLHA* accessory left hepatic artery, *LGA* left gastric artery, *SpA* splenic artery

injury to the liver [23]. Similarly, patterns of perivascular spread of tumour and involvement of adjacent lymphatics will change depending on variations of arterial anatomy [24].

Variations of smaller arterial branches of the pancreas can also have surgical relevance. In up to 8% of cases, the posterior superior pancreaticoduodenal artery originates from the hepatic artery (either common hepatic, proper hepatic or right hepatic including replaced right hepatic have been described), and a vessel of such origin would have to be ligated separately to the GDA. In the majority of cases, the inferior pancreaticoduodenal artery has its origin either posterior or to the left of the SMA, at the level of the inferior border of the neck of the pancreas, immediately proximal to the first jejunal branch of the SMA. In perhaps as many as 30% of cases, however, the inferior pancreaticoduodenal artery originates from a common trunk together with the first jejunal branch, and ligation of this common origin at the SMA risks jejunal perfusion. Similarly, the anterior inferior and posterior inferior pancreaticoduodenal arteries can arise independently, either directly from the SMA or as a common trunk with the first jejunal branch, although there is a large amount of disagreement with regards to the incidence of such a configuration [25]. Nevertheless, such an arrangement could add further confusion when looking to ligate the inferior blood supply to the head of the pancreas.

Ligation and division of the pancreaticoduodenal arcades is an essential when performing a pancreatoduodenectomy. However, there are a small number of reported cases where impaired flow through the coeliac axis (either through stenosis or kinking from inflammation/tumour infiltration) leads to a reversal of flow through the GDA and the primary arterial blood supply to the liver arising from the SMA [26, 27] resulting in hepatic ischaemia following pancreatic head resection. Temporary occlusion of the GDA and checking hepatic perfusion prior to ligation and transection of the GDA can help identify this rare variation intra-operatively.

12.7 Left Pancreatectomy: Standard Anatomy

Resection of the body and tail of the pancreas necessitates interruption of its arterial supply through ligation and division of either the splenic artery itself, or its pancreatic branches. The blood supply to the body and tail of the pancreas is highly variable. In around 1/3 of cases, the body and tail of the pancreas if supplied by a number of individual, vertical branches off the splenic artery, and in the remaining cases one or two vessels dominate and supply the gland through transverse pancreatic arterial anastomoses [28]. The dominant vertical arteries are termed dorsal pancreatic artery in the proximal body—usually arising from the proximal 1/3 of the splenic artery, but occasionally arising from the coeliac axis or common hepatic artery [29]—major pancreatic artery (arteria pancreatica magna) arising from the middle 1/3 of the splenic artery, and caudal pancreatic artery arising from the distal 1/3 or the splenic artery. Resection for malignant disease necessitates clearance of peri-vascular lymphatic tissue as well as resection of the spleen, rendering the precise configuration of the divisions of the splenic artery irrelevant for pancreatic

cancer resection. However, splenic artery anatomy and variation is of critical importance during parenchymal sparing resections for benign and ambiguous lesions.

12.8 Left Pancreatectomy: Variant Anatomy

Resection of the body and tail of the pancreas for malignancy requires division of the splenic artery at origin and splenectomy, leaving the head of the pancreas and duodenum perfused via the pancreaticoduodenal arcades. In rare cases, a connection between the coeliac axis and SMA persists into adulthood and supports the perfusion of the liver via the SMA. This variant is called 'Arc of Buhler', after the German anatomist who first described it in 1904, and is present in <0.5% of people [8, 30]. This arc typically runs close to the anatomical neck of the pancreas and is at risk of injury during parenchymal transection.

Advanced tumours of the body and tail which invade the coeliac axis or common hepatic artery can be resected together with the coeliac axis in what is called an Appleby procedure, with the entire arterial supply of the liver and stomach derived from the SMA via the pancreaticoduodenal arcades (see own chapter in this book) [31]. Modifications of this procedure including vascular reconstruction of the common hepatic artery have been reported [32], however high mortality and recurrence rates reported internationally mean such a strategy should only be attempted in exceptional cases and in expert centres. Presence of a replaced right or common hepatic artery greatly facilitates such a resection.

Pancreatic body and tail resection for benign disease, however, does not necessitate splenectomy or extended lymphadenectomy. Although the spleen can survive and retain its function following ligation of the splenic artery by maintaining its blood supply via the gastro-epiploic arcade [33], the splenic vessels can be preserved in their entirety through careful ligation of vertical branches. When lifting the pancreatic body and tail off its surrounding vascular bed in what is termed Kimura procedure, after the Japanese surgeon who first described this [34]. Dominant branches off the splenic artery need to be ligated individually and can be complicated or facilitated by variant anatomy. For example, a transverse anastomosis between the arteria pancreatica magna and caudal pancreatic arteries is present in around 25% of angiographic studies and is termed superior horizontal pancreatic artery of Popova [35], and facilitates ligation of those two branches without risking injury to the main splenic artery.

12.9 Conclusion

Variant vascular anatomy is common in pancreatic surgery and may have significant impact in the planning and execution of any given resection. Whereas major vascular abnormalities, such as a replaced hepatic artery, are usually visible on standard pre-operative imaging, abnormalities of second order branches may not be.

The example of a common origin for the IPDA and first jejunal artery demonstrates that such abnormalities can nevertheless be of huge clinical significance. A clear understanding of the development of the arterial (and to a lesser degree venous) blood supply aids understanding of anatomical variants and how to identify them intra-operatively. Abnormalities of first order hepatic arteries should prompt careful intra-operative exploration of second order arterial supply, in particular in relation to the inferior (SMA) anastomoses.

When considering extended resections or resections for locally advanced lesions, assessment of vascular anatomy becomes a critical part of pre-operative planning and may offer alternate approaches to standard resection.

Variations of venous anatomy are far less common than arterial anatomy and of less clinical relevance. Nevertheless, structures such as the gastro-colic trunk of Henle are often used as anatomical landmarks during pancreatic resection, so knowledge of their variants can aid intra-operative identification and facilitate resection.

References

1. Shinde RS, et al. Cutting-edge strategies for borderline resectable pancreatic cancer. Ann Gastroenterol Surg. 2019;3(4):368–72.
2. Assi HA, et al. Surgery versus surveillance for well-differentiated, nonfunctional pancreatic neuroendocrine tumors: an 11-year analysis of the National Cancer Database. Oncologist. 2020;25(2):e276–83.
3. Huang Q, et al. Surgical resection for metastatic tumors in the pancreas: a single-center experience and systematic review. Ann Surg Oncol. 2019;26(6):1649–56.
4. Scholten L, et al. Outcome and long-term quality of life after total pancreatectomy (PANORAMA): a nationwide cohort study. Surgery. 2019;166(6):1017–26.
5. Koike H, et al. Modelling human hepato-biliary-pancreatic organogenesis from the foregut-midgut boundary. Nature. 2019;574(7776):112–6.
6. Jennings RE, et al. Human pancreas development. Development. 2015;142(18):3126–37.
7. Larsen HL, Grapin-Botton A. The molecular and morphogenetic basis of pancreas organogenesis. Semin Cell Dev Biol. 2017;66:51–68.
8. Walker TG. Mesenteric vasculature and collateral pathways. Semin Intervent Radiol. 2009;26(3):167–74.
9. Jin GY, et al. Anatomical variations of the origin of the segment 4 hepatic artery and their clinical implications. Liver Transpl. 2008;14(8):1180–4.
10. Hikspoors J, et al. The fate of the vitelline and umbilical veins during the development of the human liver. J Anat. 2017;231(5):718–35.
11. Carneiro C, et al. All about portal vein: a pictorial display to anatomy, variants and physiopathology. Insights Imaging. 2019;10(1):38.
12. Collardeau-Frachon S, Scoazec JY. Vascular development and differentiation during human liver organogenesis. Anat Rec (Hoboken). 2008;291(6):614–27.
13. di Francesco F, et al. Pre-duodenal portal vein reconstruction at liver transplantation: the challenges and a solution. Liver Transpl. 2019;25(12):1841–4.
14. Abe H, et al. Regressing vitelline vein and the initial development of the superior mesenteric vein in human embryos. Okajimas Folia Anat Jpn. 2017;94(3):87–92.
15. Macchi V, et al. Anatomo-radiological patterns of pancreatic vascularization, with surgical implications: clinical and anatomical study. Clin Anat. 2017;30(5):614–24.

16. Bertelli E, et al. The arterial blood supply of the pancreas: a review. II. The posterior superior pancreaticoduodenal artery. An anatomical and radiological study. Surg Radiol Anat. 1996;18(1):1–9.
17. Bertelli E, et al. The arterial blood supply of the pancreas: a review. III. The inferior pancreaticoduodenal artery. An anatomical review and a radiological study. Surg Radiol Anat. 1996;18(2):67–74.
18. Katz MH, et al. Anatomy of the superior mesenteric vein with special reference to the surgical management of first-order branch involvement at pancreatoduodenectomy. Ann Surg. 2008;248(6):1098–102.
19. Kim HJ, et al. Radiologic anatomy of the superior mesenteric vein and branching patterns of the first jejunal trunk: evaluation using multi-detector row CT venography. Surg Radiol Anat. 2007;29(1):67–75.
20. Ramesh Babu CS, Sharma M. Biliary tract anatomy and its relationship with venous drainage. J Clin Exp Hepatol. 2014;4(Suppl 1):S18–26.
21. Stefura T, et al. The venous trunk of henle (gastrocolic trunk): a systematic review and meta-analysis of its prevalence, dimensions, and tributary variations. Clin Anat. 2018;31(8):1109–21.
22. Michels NA. Newer anatomy of the liver and its variant blood supply and collateral circulation. Am J Surg. 1966;112(3):337–47.
23. Gkaragkounis A, et al. Celiac trunk and hepatic arteries: anatomical variations of liver arterial supply as detected with multidetector computed tomography in 1,520 patients and its clinical importance. Clin Anat. 2019.
24. Hicks CW, et al. Management of type 9 hepatic arterial anatomy at the time of pancreaticoduodenectomy: considerations for preservation and reconstruction of a completely replaced common hepatic artery. J Gastrointest Surg. 2016;20(7):1400–4.
25. Bertelli E, et al. The arterial blood supply of the pancreas: a review. IV. The anterior inferior and posterior pancreaticoduodenal aa., and minor sources of blood supply for the head of the pancreas. An anatomical review and radiologic study. Surg Radiol Anat. 1997;19(4):203–12.
26. Bull DA, et al. Hepatic ischemia, caused by celiac axis compression, complicating pancreatoduodenectomy. Ann Surg. 1993;217(3):244–7.
27. Bramis K, et al. Whipple's procedure complicated by celiac artery stenosis: case report and review of treatment options. Cancer Res Front. 2016;2(3):427–31.
28. Covantev S, Mazuruc N, Belic O. The arterial supply of the distal part of the pancreas. Surg Res Pract. 2019;2019:5804047.
29. Pinal-Garcia DF, et al. The celiac trunk and its anatomical variations: a cadaveric study. J Clin Med Res. 2018;10(4):321–9.
30. Buhler A. Uber eine Anastomose zwischen den Stammen der Art. coeliaca und der Art. mesenterica superior. Morph Jahrb. 1904;32:185–8.
31. Egorov VI, et al. Liver blood supply after a modified Appleby procedure in classical and aberrant arterial anatomy. World J Gastrointest Surg. 2013;5(3):51–61.
32. Latona JA, et al. Modified Appleby procedure with arterial reconstruction for locally advanced pancreatic adenocarcinoma: a literature review and report of three unusual cases. J Gastrointest Surg. 2016;20(2):300–6.
33. Egorov VI, et al. Spleen-preserving distal pancreatectomy with resection of the splenic vessels. Should one rely on the short gastric arteries? JOP. 2011;12(5):445–57.
34. Kimura W, et al. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. World J Gastroenterol. 2007;13(10):1493–9.
35. Mosca S, et al. The superior horizontal pancreatic artery of Popova: a review and an anatomo-radiological study of an important morphological variant of the pancreatica magna artery. Surg Radiol Anat. 2014;36(10):1043–9.

Chapter 13
The Lymphatic System and Lymph Nodes of the Pancreas

Margot Fodor and Stefan Stättner

Take Home Messages

- Lymph node involvement (pN+) is considered an important prognostic indicator.
- The lymphatic vasculature follows the arterial blood supply of the pancreatic gland.
- Pancreatic lymph nodes are divided into anatomical regions based on the lymphatic drainage of the pancreatic gland.
- Lymph nodes surrounding the superior mesenteric artery are regarded as extra-regional and, therefore classified as distant metastases (M1).

Pearls and Pitfalls

- The prognostic role of lymph nodes can be evaluated in several ways based on the presence, number, and ratio of metastatic lymph nodes.
- Criteria for identifying pathological lymph nodes in imaging studies are unspecific.
- All imaging modalities are limited in regard to evaluation of nodal involvement.
- Extended lymphadenectomy along the superior mesenteric artery, the celiac trunk or the paraaortic region does not increase survival but adds morbidity.

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Future Perspectives
- Exploring the effect of neoadjuvant treatment on the lymphatic system.
- Research into functional and structural characteristics of the lymphatic system suggested to play a role in immune suppression.
- Developing and explore the role of biomarkers and therapeutics for lymph-angiogenesis.

13.1 Introduction

The lymphatic system of the pancreas is an intricate network of lymphatic vessels and nodes responsible for the drainage of head, neck, body, and tail of the pancreas. The complexity of this system presents variable drainage. Knowledge and understanding of the lymphatic system around the pancreas are essential for physicians in providing diagnostic and treatment strategies for patients with pancreatic pathologies. Pancreatic cancer spreads rapidly to the regional lymph nodes with a high number of metastatic lymph nodes found even in early cancers, which in itself is considered a dismal prognostic factor. In this chapter the anatomy of lymphatic system of the pancreas as well as the role of lymphadenectomy procedure are described.

13.2 The Lymph System and Its Role

Lymphatic vessels of the pancreas originate from the interlobular network in the pancreatic parenchyma. The lymphatic system is responsible for maintenance of tissue fluid homeostasis, and absorption of dietary fat. Moreover it provides leukocyte and antigen transport from tissues to lymph nodes for immune response [1]. Lymphatic capillaries are responsible for the uptake of interstitial fluids, macromolecules and leukocytes. The lymphatic capillaries are built of a single layer of endothelial cells with discontinuous intercellular junctions and lack a basement membrane [2]. Lymph and its cellular contents are transported to larger lymphatic vessels composed of also smooth muscles to facilitate flow. The afferent collecting lymphatics enter the lymph nodes where the lymph is filtered, and upon exiting the lymph nodes through the efferent collecting vessels, the lymph is transported through the major trunks of the lymphatic system, the thoracic duct, the right lymphatic trunk, and is then returned to the circulatory system [3].

13.3 The Lymphatic Network of the Pancreas

The network of lymphatic vasculature and lymph nodes is quite complex (Fig. 13.1). In the normal pancreas, the lymphatic vessels are typically located near blood vessels [4]. Although a standardized classification is still lacking, pancreatic lymph nodes are generally divided into regions based on their location around the areas of drainage of the pancreatic gland [5]. Clinicians understand the importance of anatomical lymph nodes involvement for pancreatic cancer patient prognosis, however the biological processes governing lymphatic invasion as well as therapeutic implications of targeting lymph-angiogenesis still remain open [6]. Lymph node metastases are very common in pancreatic tumors and among the most important prognostic factors.

The lymphatic network around the pancreas is not just passive tissue, it has the potential to interact dynamically with cancer cells and even with early precursor lesions (pancreatic intraepithelial neoplasia lesions). During inflammation and tumor growth, a flood of growth factors and chemokines (e.g. vascular endothelial growth factors C and D) lead to remodelling and outgrowth of lymphovascular tissue going hand in hand with cancer invasiveness (Fig. 13.1). During tumor-associated lymphangiogenesis (TALA) factors elaborated by tumor cells and other supporting cell types of the tumor microenvironment, such as cancer-associated fibroblasts (CAFs), or tumor-associated macrophages (TAMs), interact with cognate receptors on the lymphatic endothelium both locally and in lymph nodes to influence lymphangiogenesis, lymph node metastasis, and tumor progression. Studies of human pancreatic cancer tissues have identified a role for TALA in lymph node metastasis and patient outcomes [7]. High lymphatic vessel density (LVD) in pancreatic ductal adenocarcinoma (PDAC) head tumors was shown to predict increased lymph node metastasis and decreased survival. They also showed increased lymphatic vessel density within metastatic lymph nodes which was associated with unfavourable tumor differentiation status and more lymph node metastasis [6]. These data highlight the importance of peripancreatic lymphatics in the progression and metastasis of pancreatic cancer and their potential utility as both a predictor of patient outcomes and a possible therapeutic target [6, 8].

13.4 Clinical-Anatomical Classification

Many reports have described the peripancreatic lymphatic system. Certain authors have named lymph groups according to their location around the pancreas describing five main groups: superior, inferior, anterior, posterior and splenic [9, 10]. Other authors have developed numerical classifications based on lymph node spreading describing 11 nodal areas, forming four lymphatic pathways around the head of the pancreas [11–13]. Further analyses provided a description of eight lymphatic pathways running towards the abdomino-aortic (para-aortic) lymph nodes, reporting three lymphatic pathways in the anterior surface of the head, three in the posterior

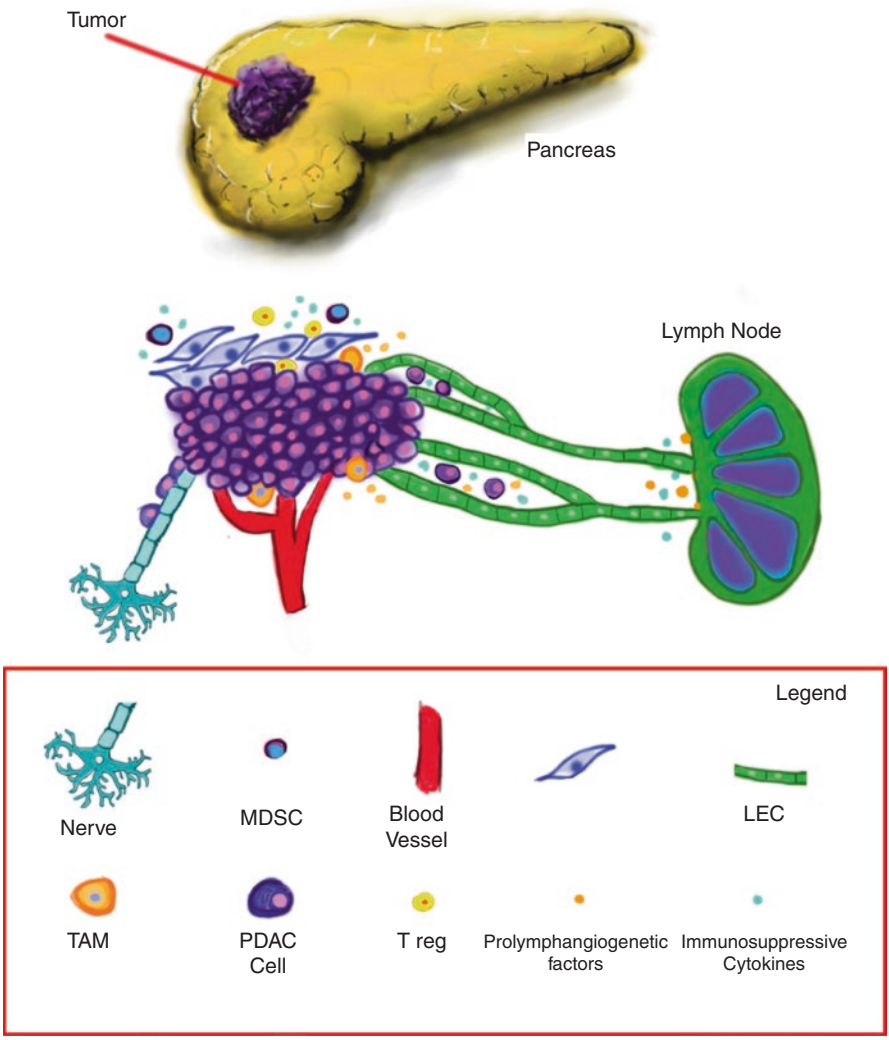

Fig. 13.1 Pancreatic tumor microenvironment and lymph node metastasis. Cells of the tumor microenvironment are essential contributors to tumor growth, lymphatic invasion, and lymph node metastasis. Cancer associated fibroblasts (CAFs) and tumor associated macrophages (TAMs) secrete pro-lymphangiogenic factors and proteases needed for lymphangiogenesis and metastasis. Lymphatic vessels act as conduits not only for tumor cell metastasis, but also for immunosuppressive cell and cytokine transport to lymph nodes. Nerves are also another route for pancreatic tumor metastasis and can communicate with lymphatic vessels to facilitate tumor metastasis from one network to the other. *PDAC* pancreatic ductal adenocarcinoma, *LEC* lymphatic endothelial cells, *CAF* cancer-associated fibroblast, *TAM* tumor-associated macrophage, *Treg* regulatory T-cell, *MDSC* myeloid-derived suppressor cell. (Adapted from Fink DM et al. [6])

surface and two major lymphatic routes in the left half of the pancreas [14]. Finally, the Japanese Pancreatic Society (JPS) developed an anatomical classification dividing regional and juxta-regional lymph nodes based on data from 18,629 cases of carcinoma of the pancreas [9, 10], establishing a comprehensive nomenclature of the different lymph nodes stations relevant for pancreatic cancer surgery (Fig. 13.4) [15–17]. This nomenclature has been internationally adopted and allowed to set international standards for the extent of lymphadenectomy in pancreatic cancer. Based on this nomenclature the international study group on pancreatic surgery (ISGPS) released consensus recommendations in 2014 [18]. The anatomical localization of regional lymph nodes according to the pancreatic regions is shown in Table 13.1 and Figs. 13.2, 13.3, and 13.4. An alternative route is described, where

Table 13.1 Station numbers and states of lymph nodes related to the pancreas [19], see corresponding visual description in Fig. 13.4

Number	Name
1	Right cardial lymph node
2	Left cardial lymph node
3	Lymph nodes along the lesser curvature of the stomach
4	Lymph nodes along the greater curvature of the stomach
5	Suprapyloric lymph nodes
6	Infrapyloric lymph nodes
7	Lymph nodes along left gastric artery
8a	Lymph nodes in the anteriosuperior group along common hepatic artery
8p	Lymph nodes in the posterior group along common hepatic artery
9	Lymph nodes around coeliac artery
10	Lymph nodes in the splenic hilum
11p	Lymph along the proximal superior pancreaticoduodenal artery
11d	Lymph along the distal superior pancreaticoduodenal artery
12a	Lymph along the hepatic artery
12p	Lymph along portal vein
12b	Lymph along the bile duct
13a	Lymph along on the posterior aspect of the superior portion of head of the pancreas
13b	Lymph along on the posterior aspect of the inferior portion of the head of the pancreas
14p	Lymph along the proximal superior mesenteric artery
14d	Lymph along the distal superior mesenteric artery
15	Lymph along the
16a1	Lymph along the aortic hiatus of the diaphragm
16a2	Lymph along the abdominal aorta (from the superior margin of the celiac trunk to the inferior margin of left renal vein)
16b1	Lymph along the abdominal aorta (from the inferior margin of left renal vein to the superior margin of inferior mesenteric artery)
16b2	Lymph along the abdominal aorta (from the superior margin of inferior mesenteric artery to the aortic bifurcation)
17a	Lymph along on the anterior surface of the superior portion of head of the pancreas
17b	Lymph along on the anterior surface of the inferior portion of head of the pancreas
18	Lymph along on the inferior margin of the pancreas

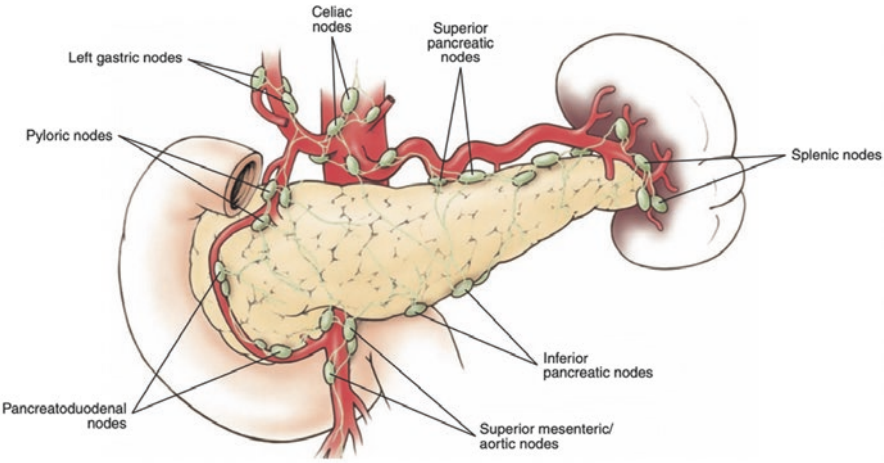

Fig. 13.2 Location of lymph nodes surrounding the pancreas. There is individual variation in the location of lymph nodes. Lymphatic drainage of body and tail of the pancreas drains into the nodes at the splenic hilum and follows the splenic artery to the celiac node, the principal nodal group. On the other side, the lymphatic drainage of the anterior cephalad portion of the head of the pancreas follows lymphatic vessels along the anterior superior pancreaticoduodenal artery to the pyloric, or sub-pyloric nodal group, consisting of several lymph nodes along the gastroduodenal artery where it originates from the common hepatic artery. This nodal group is located behind the pylorus and anterio-superior to the head of the pancreas. Regarding the posterior side, the cephalad portion drains into the nodes along the bile duct behind the portal vein in the hepatoduodenal ligament and arriving at the hepatic hilar node [19]. (Reproduced with permission of the publishers [37])

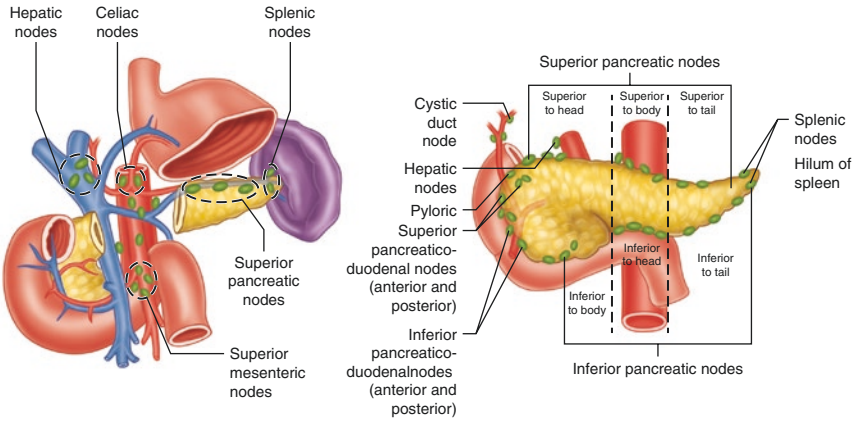

Fig. 13.3 Lymph nodes draining the pancreas seen from different angles. Typical location of lymph nodes surrounding the pancreas. There is individual variation in the location of lymph nodes. Standard lymphadenectomy should include supra and infra-pyloric nodes (stations 5, 6), nodes to the right of the hepatoduodenal ligament (stations 12b1, 12b2, and 12c), anterior and posterior pancreatico-duodenal nodes (stations 17a, 17b, 13a, and 13b), nodes to the right of the superior mesenteric artery (stations 14a and 14b), and anterior to the common hepatic artery (station 8a). Lymph nodes stations 13 and 17 are included within the pancreaticoduodenal groove, and therefore always removed with the specimen [26]. Extended lymphadenectomy involves removal of all the lymph nodes stations described in standard lymphadenectomy and, in addition, perineural plexus and lymph nodes along the coeliac axis, superior mesenteric artery and para-aortic lymph nodes [21]. (Reproduced with permission of the publishers [38])

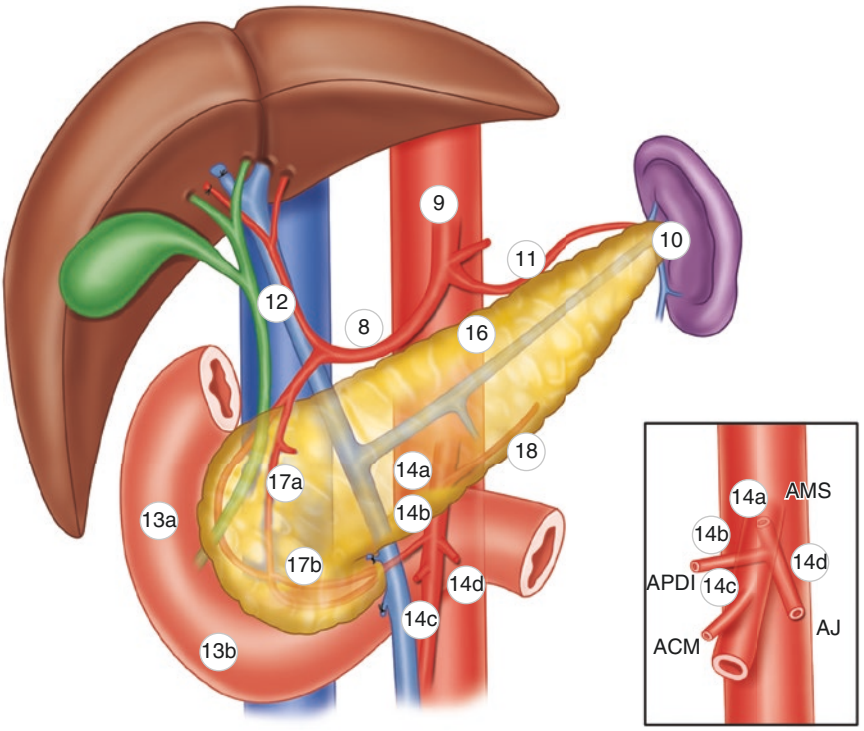

Fig. 13.4 Anatomical lymph node locations according to the JPS classification. There is individual variation in the location of lymph nodes. Insert: Subdivision of Group 14: *AMS* superior mesenteric artery, *AJ* jejunal artery, *APDI* inferior pancreaticoduodenal artery, *ACM* medial colic artery. (Reproduced with permission of the publishers [17])

drainage follows the posterior superior pancreaticoduodenal artery to the pyloric node. These described pathways, also defined as superior or ascending pathways, drain into the celiac node as their principal node. Regarding the caudal portion of the head of the pancreas and the uncinate process, lymphatic drainage follows the inferior pancreaticoduodenal vessels to the superior mesenteric artery lymph nodes and drains into the retroperitoneal paraaortic lymph nodes [19]. This pathway is defined as inferior or descending pathway [20].

Lymph nodes involvement is considered one of the most important prognostic indicators in pancreatic cancer while other important factors influencing survival include tumor histology, size, status of resection margins, grade and lymphovascular invasion [21]. The majority of lymph nodes metastases is detected at the peripancreatic nodal group, including the anterior and posterior peripancreatic nodes, the pancreaticoduodenal, pyloric and inferior nodes. The size of the tumor is correlated with the rate of positive lymph nodes, larger tumors frequently metastasize into para-aortic lymph nodes (T3 in up to 11% and T4 in up to 33%) [15]. There are no data to support that patients undergoing either the en-bloc dissection technique or the staged dissection are doing any better. The authors prefer the en-bloc technique, leaving all lymphatic tissue on the specimen.

13.4.1 Radiologic Imaging

In radiologic diagnostic imaging morphologic differentiation between metastatic lymph nodes enlargement from normal or reactive cases should be performed. A lymph node of more than 10 mm is diagnosed as lymph node enlargement, however this is not always related to metastasis, as even lymph nodes ≤5 mm may already be infiltrated by micro-metastasis. Furthermore, CT scans can detect malignancy due to contrast enhancement. Usually, normal or reactive lymph nodes display homogeneous enhancement despite enlargement [19, 20]. Criteria to try to improve sensitivity and specificity in predicting nodal metastases have been analysed (see also other chapters on imaging in this book). Low-density nodes with irregular margins are highly suspect but they are not sensitive enough to detect the majority of metastatic nodes. Lymph nodes larger than 5 mm in the inferior pancreatic nodal group increase the sensitivity to detect nodal metastasis. Enlarged nodes in the periportal and common hepatic nodal groups are non-specific and can also be seen in patients with jaundice and stents in place, chronic pancreatitis or node-negative pancreatic cancer. Nevertheless, detailed knowledge of preoperative scans is mandatory before resection to guide surgery and potentially avoid futile laparotomy. Radiomics for predicting lymph node metastasis is currently pathing its way into clinical practice [22].

13.4.2 Sentinel Lymph Node

The sentinel lymph node technique for pancreatic cancer has been evaluated to permit the preoperative identification of patients with lymphatic dissemination for better staging and to avoid unnecessary morbidity. However, attempts to map pancreatic lymphatic drainage using methylene blue or indocyanine green injection in the tumor as well as lymphoscintigraphy with intratumoral injection of a radiotracer (Technetium 99 labelled nanocolloid) via endosonography have been reported, to map the individual lymphatic spread [23–25] have not been successful. Thus, these methods have not found a role in management of pancreatic cancer.

13.5 Tumors of the Pancreatic Head

For cancers of the pancreatic head, pancreaticoduodenectomy is the only potential curative option. Due to the prognostic power of lymph nodes involvement, lymphadenectomy is considered an essential step of pancreaticoduodenectomy. Standard lymphadenectomy should include supra and infra-pyloric nodes, nodes to the right of the hepatoduodenal ligament, anterior and posterior pancreatico-duodenal nodes, nodes to the right of the superior mesenteric artery and anterior to the common hepatic artery (Figs. 13.2, 13.3, 13.4, 13.5, and 13.6). Lymph nodes stations 13 and

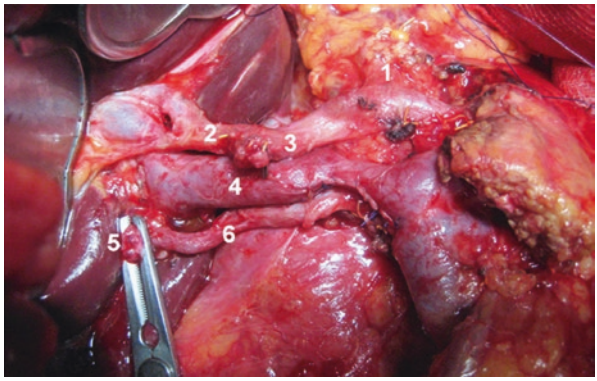

Fig. 13.5 Lymph node dissection in the hepatoduodenal ligament. Left gastric artery (1), proper hepatic artery (2), common hepatic artery (3), portal vein (4), interrupted common hepatic duct (5) and an aberrant right hepatic artery (6). (Reproduced with permission of the publishers [26])

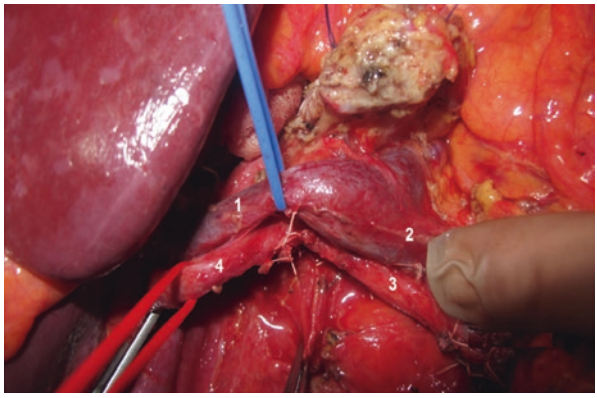

Fig. 13.6 Lymphadenectomy along the right side of the superior mesenteric artery. (3): portal vein (1), superior mesenteric vein (2) and an aberrant common hepatic artery extending from the superior mesenteric artery (3). (Reproduced with permission of the publishers [26])

17 are included within the pancreaticoduodenal groove, and therefore always removed with the specimen [26].

Extended lymphadenectomy involves removal of all the lymph nodes stations described in standard lymphadenectomy and, in addition, would remove perineural plexus and lymph nodes along the coeliac axis, superior mesenteric artery and paraaortic lymph nodes [21]. However, complete resection of the lymph nodes around the superior mesenteric artery leads to higher morbidity, in particular postoperative diarrhoea, which is markedly more common in patients in whom nerve tissue surrounding the superior mesenteric artery was cleared circumferentially. Lymph nodes in this area are internationally considered extra-regional and, therefore, distant metastases (M1). However, extended lymphadenectomy is technically feasible but biologically rather questionable. It may play a role after neoadjuvant therapy with adequate response but must then be considered as resection of distant metastatic disease. Moreover, in patients with isolated lymph nodes recurrences during surveillance after pancreatic cancer resection, surgical re-resection can be considered [27].

Standard lymphadenectomy is a guide for surgeons when operating on patients with resectable pancreatic adenocarcinoma. According to literature and expert opinion, extended lymphadenectomy does not benefit long-term survival and might lead to higher levels of morbidity [28]. Nevertheless, the appropriate extent of lymph node dissection and its beneficial effects are still biologically controversial because the detailed pattern of lymph node metastasis spread in pancreatic cancer remains unclear [29].

The number of lymph nodes required to minimize the risk of the stage migration phenomenon is proposed to be between 10 and 15 [30]. The standard lymphadenectomy should regularly provide between 13 and 17 lymph nodes, the extended lymphadenectomy between 20 and 40 lymph nodes to ensure adequate pathologic staging and prognostication [18, 27]. Data suggest, that high volume centers reach a higher yield of lymph nodes, this might be due to more standardised pathology reporting or more extensive dissection [31].

13.6 Tumors of the Body and Tail

Regarding tumors situated in body or tail, those lymph nodes attached to the pancreas in the resected specimen are most frequently involved (Fig. 13.7). In this case two or three positive nodes have an equal survival to those patients with an N0

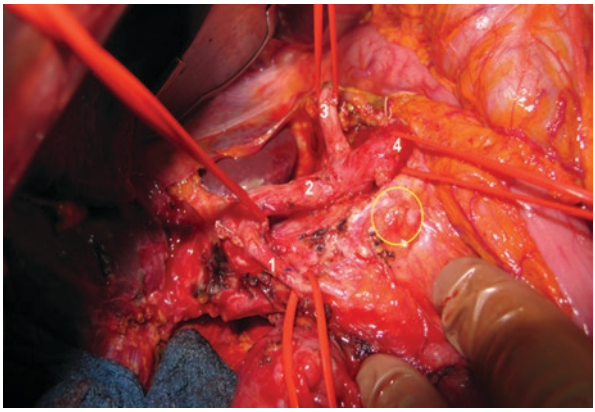

Fig. 13.7 Tumor (yellow circle) localized in the body of the pancreas. The lymphadenectomy includes lymph nodes in station 9 (around the celiac artery)–gastroduodenal artery (1), common hepatic artery (2), left gastric artery (3), splenic artery (4). Standard lymphadenectomy during pancreatectomy for patients with pancreatic adenocarcinoma in the body or tail includes lymph nodes in stations 10 in the hilum of the spleen, 11 along the splenic artery, and 18 along the inferior border of the body and tail of the pancreas. Hence, splenectomy is usually indicated to obtain adequate excision of both the primary tumor and lymph nodes [18]. Station 9 is only suggested to be included in the resection when tumors are confined to the body of the gland. Reproduced with permission of the publishers [26]

situation. Directly attached lymph nodes and peripancreatic nodes have to be removed to achieve best oncological outcome. Comparable to the setting of pancreatic head resection, more extended lymphadenectomy is not recommended as this is associated with increased morbidity without proven oncological benefit. Total pancreatectomy is indicated in case of multifocal pancreatic cancer as well as multiple metastases in the pancreas. Moreover, it may be necessary to achieve a tumor-free resection margin and R0 situation in centrally localized tumors of the pancreatic body, avoiding pancreatic transection with the risk of tumor cell spilling. The volume of lymph nodes dissection in total pancreatectomy comprises standard lymphadenectomy in pancreaticoduodenectomy and distal pancreatectomy.

13.6.1 Neoadjuvant Treatment and Lymph Node Yield

Although surgery followed by adjuvant chemotherapy still represents standard of care for resectable pancreatic cancer, approximately 50% of patients are unable to receive adjuvant treatment due to postoperative complications. Recent studies evaluated the role of neoadjuvant chemotherapy, which has advantages, including downstaging of nodal disease, improved operability, and greater achievement of negative surgical margins. Randomized trials will be needed to evaluate neoadjuvant chemotherapy as new standard for patients with malignant resectable pancreatic neoplasm [32]. Neoadjuvant chemotherapy might influence the number of resected lymph nodes in the pathological specimen. An analysis of the national cancer database in the United States showed that neoadjuvant treatment in PDAC stages I-III improved survival, the minimum number of lymph nodes that need to be removed to reach better survival was 8 (versus 12 lymph nodes in patients who had adjuvant chemotherapy) [33]. Another study from MD Anderson Cancer Center showed similar results, patients receiving neoadjuvant treatment in resectable disease had a lower rate of positive lymph nodes and better overall survival. Additionally, tumor regression in metastatic lymph nodes was associated with better survival as well, probably demonstrating a biological benefit [34].

The Dutch PREOPANC study randomized resectable and borderline resectable PDAC patients to either first line surgery or neoadjuvant chemo-radiotherapy. They reported a higher rate of R0 resections and less pathologic lymph nodes in the neoadjuvant group (33% N1 versus 78%), which was a significant difference; nevertheless, the study failed to show a survival benefit [35].

13.7 Conclusion

Pancreatic cancer is a highly lethal disease for which surgical resection offers the only hope for cure [36]. The lymphatic drainage of the pancreas involves a complex arrangement of vessels and lymph nodes. A detailed knowledge of the pancreatic

lymphatics is essential to surgeons treating patients with pancreatic pathologies. The identification of positive lymph nodes correlates with a poorer prognosis. Additionally, variation in the metastasis of the tumor may exist, especially with occurrence of lymph nodes obstruction. All of these points are especially important for surgeons who are performing lymph nodal dissection for pancreatic pathologies.

References

1. Stacker SA, Williams SP, Karnezis T, Shayan R, Fox SB, Achen MG. Lymphangiogenesis and lymphatic vessel remodelling in cancer. Nat Rev Cancer. 2014;14(3):159–72.
2. Baluk P, Fuxe J, Hashizume H, Romano T, Lashnits E, Butz S, et al. Functionally specialized junctions between endothelial cells of lymphatic vessels. J Exp Med. 2007;204(10):2349–62.
3. Alitalo A, Detmar M. Interaction of tumor cells and lymphatic vessels in cancer progression. Oncogene. 2012;31(42):4499–508.
4. O'Morchoe CC. Lymphatic system of the pancreas. Microsc Res Tech. 1997;37(5–6):456–77.
5. Cesmebasi A, Malefant J, Patel SD, Du Plessis M, Renna S, Tubbs RS, et al. The surgical anatomy of the lymphatic system of the pancreas. Clin Anat. 2015;28(4):527–37.
6. Fink DM, Steele MM, Hollingsworth MA. The lymphatic system and pancreatic cancer. Cancer Lett. 2016;381(1):217–36.
7. Kurahara H, Takao S, Shinchi H, Maemura K, Mataki Y, Sakoda M, et al. Significance of lymphangiogenesis in primary tumor and draining lymph nodes during lymphatic metastasis of pancreatic head cancer. J Surg Oncol. 2010;102(7):809–15.
8. Shen CN, Goh KS, Huang CR, Chiang TC, Lee CY, Jeng YM, et al. Lymphatic vessel remodeling and invasion in pancreatic cancer progression. EBioMedicine. 2019;47:98–113.
9. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas area. Cancer. 1978;41(3):880–7.
10. Renard Y, Perrenot C, Labrousse M, Avisse C, Rhaiem R, Piardi T, et al. Exploration of peripancreatic lymphatic pathways in a live porcine model. Ann Anat. 2019;225:57–64.
11. Kayahara M, Nagakawa T, Kobayashi H, Mori K, Nakano T, Kadoya N, et al. Lymphatic flow in carcinoma of the head of the pancreas. Cancer. 1992;70(8):2061–6.
12. Nagakawa T, Konishi I, Ueno K, Ohta T, Kayahara M. A clinical study on lymphatic flow in carcinoma of the pancreatic head area—peripancreatic regional lymph node grouping. Hepato-Gastroenterology. 1993;40(5):457–62.
13. Nagakawa T, Kobayashi H, Ueno K, Ohta T, Kayahara M, Miyazaki I. Clinical study of lymphatic flow to the paraaortic lymph nodes in carcinoma of the head of the pancreas. Cancer. 1994;73(4):1155–62.
14. Deki H, Sato T. An anatomic study of the peripancreatic lymphatics. Surg Radiol Anat. 1988;10(2):121–35.
15. Isaji S, Kawarada Y. [Evaluation of classification of pancreatic cancer by the Japan Pancreas Society and Union Internationale Contre le Cancer and proposal for a new international classification]. Nihon Geka Gakkai Zasshi. 2000;101(2):205–11.
16. Yamada S, Fujii T, Hirakawa A, Kanda M, Sugimoto H, Kodera Y. Lymph node ratio as parameter of regional lymph node involvement in pancreatic cancer. Langenbeck's Arch Surg. 2016;401(8):1143–52.
17. Sun W, Leong CN, Zhang Z, Lu JJ. Proposing the lymphatic target volume for elective radiation therapy for pancreatic cancer: a pooled analysis of clinical evidence. Radiat Oncol. 2010;5:28.
18. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.

19. Kanehara. Classification of pancreatic carcinoma. 4th English edition. Japan Pancreas Society; 2017.
20. Chusilp Charnsangavej MAM. Pathways of regional spread in pancreatic cancer. Dynamic radiology of the abdomen, normal and pathologic anatomy. Springer; 2005. p. 595–606.
21. Dasari BV, Pasquali S, Vohra RS, Smith AM, Taylor MA, Sutcliffe RP, et al. Extended versus standard lymphadenectomy for pancreatic head cancer: meta-analysis of randomized controlled trials. J Gastrointest Surg. 2015;19(9):1725–32.
22. Li K, Yao Q, Xiao J, Li M, Yang J, Hou W, et al. Contrast-enhanced CT radiomics for predicting lymph node metastasis in pancreatic ductal adenocarcinoma: a pilot study. Cancer Imaging. 2020;20(1):12.
23. Beisani M, Roca I, Cardenas R, Blanco L, Abu-Suboh M, Dot J, et al. Initial experience in sentinel lymph node detection in pancreatic cancer. Rev Esp Med Nucl Imagen Mol. 2016;35(5):287–91.
24. van Manen L, Handgraaf HJM, Diana M, Dijkstra J, Ishizawa T, Vahrmeijer AL, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. J Surg Oncol. 2018;118(2):283–300.
25. Vuijk FA, Hilling DE, Mieog JSD, Vahrmeijer AL. Fluorescent-guided surgery for sentinel lymph node detection in gastric cancer and carcinoembryonic antigen targeted fluorescent-guided surgery in colorectal and pancreatic cancer. J Surg Oncol. 2018;118(2):315–23.
26. Kostov D. Recent advances in pancreatic cancer. Lymphadenectomy in pancreatic cancer surgery: avid science; 2017.
27. Niesen W, Hank T, Büchler M, Strobel O. Local radicality and survival outcome of pancreatic cancer surgery. Ann Gastroenterol Surg. 2019;3(5):464–75.
28. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012;19(3):230–41.
29. Kanda M, Fujii T, Nagai S, Kodera Y, Kanzaki A, Sahin TT, et al. Pattern of lymph node metastasis spread in pancreatic cancer. Pancreas. 2011;40(6):951–5.
30. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006;13(9):1189–200.
31. Eskander MF, de Geus SW, Kasumova GG, Ng SC, Al-Refaie W, Ayata G, et al. Evolution and impact of lymph node dissection during pancreaticoduodenectomy for pancreatic cancer. Surgery. 2017;161(4):968–76.
32. Motoi F, Kosuge T, Ueno H, Yamaue H, Satoi S, Sho M, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). Jpn J Clin Oncol. 2019;49(2):190–4.
33. Macedo FI, Picado O, Hosein PJ, Dudeja V, Franceschi D, Mesquita-Neto JW, et al. Does neoadjuvant chemotherapy change the role of regional lymphadenectomy in pancreatic cancer survival? Pancreas. 2019;48(6):823–31.
34. Roland CL, Yang AD, Katz MH, Chatterjee D, Wang H, Lin H, et al. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. Ann Surg Oncol. 2015;22(4):1168–75.
35. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020;38(16):1763–73. JCO1902274.
36. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015;27(4):332–48.
37. Kooby DA. Pancreas and duodenum. In: Wood WC, Staley C, Skandalakis JE, editors. Anatomic basis of tumor surgery. 2nd ed. Berlin: Springer; 2010. p. 562.
38. Cancer AJCo. AJCC cancer staging atlas. New York: Springer; 2006.

Part IV
Understanding Disease Biology

Chapter 14
The Hallmarks of Pancreatic Cancer

Alexander Ioannis Damanakis, Florian Gebauer, Felix Popp, and Christiane Bruns

Take Home Messages

- There are four driver genes for pancreatic cancer: *KRAS oncogene*, *CDKN2A, p53*, and *SMAD4 tumor suppressor genes*.
- Pancreatic carcinomas are genetically very heterogeneous and show on average between 60 and 70 genetic alterations which influence a variety of signaling pathways.
- There are genetic mutations known to predispose patients carrying them to pancreatic cancer. BRCA2, p16/CDKN2A, STK11, PRSS1, PALP2, FANCC and FANCG and ATM belong to the most important ones.
- The stroma with its consecutive impaired perfusion and tumor specific microenvironment is to a large part considered responsible for the often poor response to chemotherapy.
- Interactions between cancer associated fibroblasts and PDAC cells are responsible for intra-tumoral heterogeneity and influence the pro-invasive and pro- metastatic capabilities of cancer cells.

Future Perspectives

- Individual tumor therapy after genomic sequencing of PDACs.
- Possible emerging role of targeted therapies in PDACs.
- Further improved understanding of intra- and inter-tumoral heterogeneity by single cell analysis and enhanced understanding of PDAC architecture.
- Identifying subgroups based on genomic analyses to allow risk stratification for patients at high risk for PDAC.

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14.1 Introduction

Pancreatic carcinoma is a major therapeutic challenge. Despite complex multimodal treatment approaches, approximately 90% of patients die from this disease. In the last few years, the better processing of genetic alterations in particular has improved the understanding of the pathogenesis of pancreatic carcinoma. In the following, we provide an overview of the molecular properties of pancreatic cancer and put them in line with the hallmarks of cancer (Fig. 14.1) as defined by Weinberg and Hanahan. Both authors suggested in their 2011 updated version eight hallmarks of cancer: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism and evading immune destruction. The specific characteristics of pancreatic carcinoma will be highlighted and explained to provide a dedicated overview about the current understanding of molecular mechanisms leading to pancreatic cancer.

14.1.1 Precursor Lesions and the Pancreatic Cancer Progression Model

The most common form of pancreatic carcinoma is the adenocarcinoma (90%). According to current knowledge, the malignant transformation of "healthy" pancreatic cells into an invasive carcinoma is based in a progression model analogous to

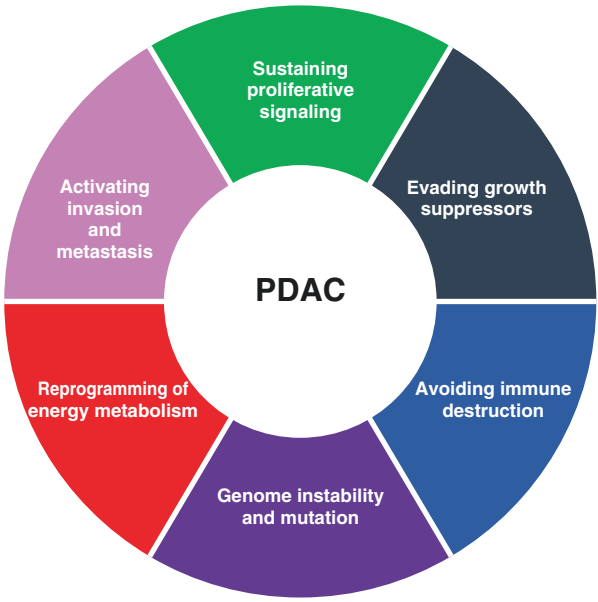

Fig. 14.1 Hallmarks of pancreatic cancer. Modified Hallmarks of Pancreatic Cancer, adjusted according to [17]. (Figure created by Damanakis A. I., permission granted)

the adenoma-carcinoma sequence in colon adenocarcinoma. In pancreatic ductal adenocarcinoma, the process is proceeded by various precursor lesions. The most important are *pancreatic intraepithelial neoplasias* (PanIN), *intraductal mucinous neoplasias* (IPMNs) and *mucinous cystic neoplasias* (MCNs).

The majority of classical ductal adenocarcinomas develop through the PanIN progression model (Fig. 14.1). A prerequisite for this seems to be that acinar cells go through a process that is called acinar-to-ductal metaplasia (ADM) (Fig. 14.1). It is triggered by tissue damage, inflammation or stress, among others, and it describes the transformation of an acinar phenotype to a more ductal (epithelial) one. It reflects the plasticity of acinar cells and is a physiological process. Nevertheless, ADM may lead to the development of PanINs as it is known that during ADM cells are more susceptible to oncogenic genetic insults such as *KRAS* activation [1]. PanINs can only be detected microscopically and have a diameter of <5 mm. PanINs are divided into *low-grade* (formerly PanIN 1A,1B, PanIN 2) and *high-grade* (formerly PanIN 3) according to histological criteria [2]. The low-grade PanINs are characterized first by hyperplasia and then by increasing atypia (Fig. 14.2). *High-grade* PanINs are carcinomas at the cellular level that do not cross the basement membrane (according to the concept of the carcinoma in situ) due to findings such as cancelled cell polarity, heaped mitoses, and nuclear irregularities [5]. They can often be detected in pancreatic carcinoma specimen. The low-grade PanINs contain genetic alterations typical of pancreatic carcinoma, the prevalence of which increases with the degree of atypia [3] (Fig. 14.2). Precursor lesions are covered in

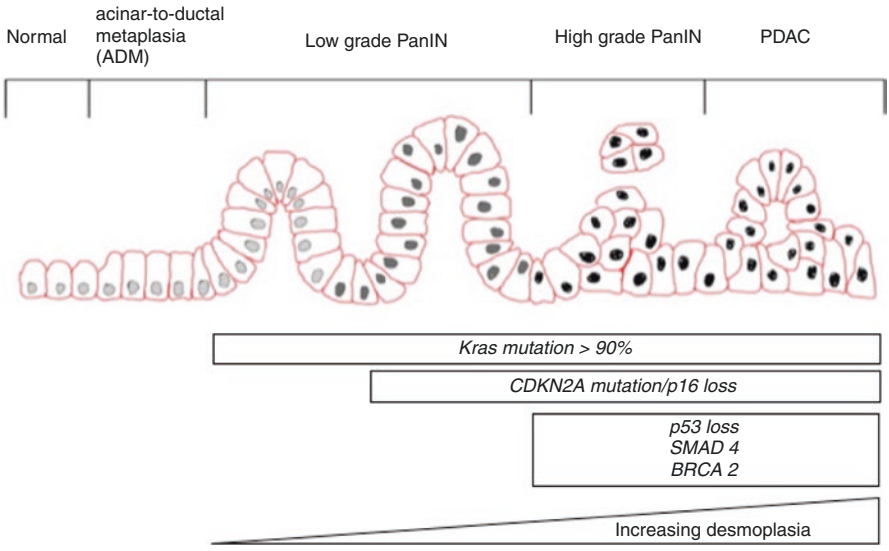

Fig. 14.2 Progression model from intraepithelial neoplasia to ductal adenocarcinoma of the pancreas. Overview of progression model from intraepithelial neoplasia to ductal adenocarcinoma. (Modified after Vincent A et al., Lancet 2011 and Tanaka S, Ann Surg Oncol 2016 [3, 4], created by Damanakis A. I., permission granted)

more detail in other chapters. Their common endproduct is the invasive cancer. The molecular hallmarks of pancreatic cancer will be discussed in the following.

14.1.2 Sustaining Proliferative Signaling in Pancreatic Cancer

Pancreatic carcinomas are genetically very heterogeneous and show on average between 60 and 70 genetic alterations which influence a variety of signaling pathways [6, 7]. Four so called *driver* genes for the development of pancreatic adenocarcinoma are described in the literature. The most common mutation in ductal adenocarcinoma found in >90% of tumors is the mutation of the *KRAS oncogene*. Mutation in the RAS gene are found in up to a third of human cancer. The loss of the binding capability for GTPases leads to the accumulation of active RAS in the cell and thus a permanent growth signal. Still, a KRAS mutation is not required for PDAC development. Even if 99% of PanIN-1 show a KRAS mutation, no more than 95% PDACs have a KRAS mutation. The other three driver genes, *CDKN2A, p53*, and *SMAD4,* are all tumor suppressor genes and mutated in about 90%, 70%, and 50% of carcinomas, respectively (also see Sect. 14.1.4) [8]. Development of PDAC was long seen as following a particular sequence of genetic alterations. Also, PDAC progression was supposed to be always gradual because the mutations were acquired independently [9]. However, recent research could show that cancer development can originate in a single event in which thousands of chromosomal rearrangements in one or a few chromosomes occur in certain genomic areas. This process is pushing the cellular ability for survival to an edge and subsequent aberrant repair of the "destructions" leads, among others, to imperfect DNA repair or DNA replication. Thus laying the groundwork for cancer development [10]. This mutational process is called *chromothripsis*. Notta et al. could show that chromothripsis has a high prevalence in PDAC thus challenging the belief of gradual cancer development [9]. This finding supports the *catastrophic* model of PDAC progression as was proposed by Real et al. in 2003 [11].

The activating mutation of *KRAS* contributes decisively to the progression to invasive carcinoma and enables early metastasis. Further research could show, that also the "dosage" of *KRAS* mutation plays a critical role in PDAC development and in individual PDACs biology. Mueller et al. analyzed oncogenic dosage variation and the phenotypic diversification of PDAC. They could show that an increase in mutant *KRAS* can be found in low grade PanINs. Increased mutant KRAS could be linked to early tumorigenesis and metastasis via effects on cell morphology and plasticity, histopathology and clinical outcome. Also, the most aggressive undifferentiated phenotypes were linked to highest mutant *KRAS* dosages [12]. The combination of mutant KRAS dosage and abovementioned chromothripsis are thus supposed to represent decisive steps for PDAC development [13].

Even if prognostic information can only be derived partly of driver gene mutations, it is assumed that the mutation of *KRAS is* a marker for a dismal prognosis. The loss of *SMAD4* is also associated with the occurrence of invasive tumor stages with vascular invasion, lymph node and distant metastases, and early local

recurrences [14]. Recently, some studies using whole-exome sequencing have described new gene mutations that affect different cell regulatory mechanisms such as histone modification, DNA repair, or axonal guidance [15]. With regard to the precursor lesions PanIN and IPMN, as well as MCN, it was demonstrated that typical genetic alterations are present at early and later points in time [8]. More than 90% of PanIN lesions have an "early" *KRAS* mutation which is already present in *low-grade* PanINs. This also applies to the *CDKN2A* changes. In contrast, mutations in the *SMAD4* and *p53* genes are rather late events that can be detected in *high-grade* PanIN and invasive carcinomas (see also Fig. 14.1). The IPMNs and MCNs show *KRAS* mutations in approximately 70% [4]. Whole exome sequencing of PanINs and adjacent adenocarcinomas showed a very similar distribution of mutations which supports the idea of the progression model from PanIN to a carcinoma following the adenoma-carcinoma sequence in colon carcinoma [8]. Autopsy studies could show that a lower number of driver gene alterations was positively correlated to disease free survival, overall survival and metastatic burden at autopsy.

Box 14.1 Gene Dosage
The number of copies of a particular gene in a genome is called the "gene dosage". Gene insertions or deletions cause changes in gene dosage. Those structural variations are called "copy number variations" (CNV) when they represent sections of the genome that are repeated. The number of repeats in the genome varies between individuals. In general, CNVs account for the variation that is necessary in the population. But they can also determine a disease phenotype, e.g. by *focal gain* or *arm level gain* structural variations that cause an increase in gene dosage.

14.1.3 Avoiding Immune Destruction

A decisive mechanism for tumor progression in PDAC seems to be the ability of immune modulation meaning immunosuppression within the microenvironment. Already in early phases of tumor development, regulatory inhibitory T-cells are recruited into the stroma and block the T-cell-mediated antitumoral immunity. *KRAS* activation triggers the differentiation of myeloid progenitor cells into myeloid suppressor cells (MDSC) by releasing the granulocyte-monocyte colony-stimulating factor (GM-CSF) which has an immunosuppressive effect on cytotoxic CD8+ T cells. This leads to an overall immunological imbalance that favors the further development of malignant cells [16]. Also, *KRAS* promotes inflammation by the release of cytokines from PanIN precoursor lesions that causes signaling pathways for cell survival, such as STAT3, to be activated. The special role of the immunosuppressive microenvironment is decisively influenced by hyperactivated focal adhesion kinase (FAK1) in the neoplastic cells. FAK1 activation correlates to a lower number of tumor-infiltrating CD8+ cytotoxic T lymphocytes and high levels of total stromal collagen [17].

14.1.4 Evading Growth Suppressors

Three of the abovementioned driver genes are so called tumor suppressor genes (*CDKN2A, p53, SMDA4*). Their inactivation is necessary to eliminate mechanisms that under normal circumstances limit cell growth and proliferation. Tp53 tumor suppressor gene plays a pivotal role in PDAC carcinogenesis with a mutation found in approximately 75–85% of human PDAC. P53 predominantly acts as a transcriptional factor reacting to DNA damage, hypoxia and other cellular stress factors [18]. Loss of heterozygosity of Tp53 is associated with a progression from PanIN to PDAC. There is no need for a total inactivating mutation of Tp53 as oncogenic gains of function can suffice to hinder p53 in exerting its task of regulating the G1/S checkpoint, maintenance of G2/M arrest and apoptosis initiation [19, 20]. Recently, one way of exerting p53's tumor suppressing capabilities was identified as the activation of the Ptpn14 gene which inactivates the oncoprotein YAP. This mechanism is referred to as the p53-Ptpn14-Yap axis in PDAC [20].

14.1.4.1 *CDKN2A*

CDKN2A produces two mRNAs which encode for $p16^{INK4A}$ and $p19^{ARF}$. It is assumed that both may lead to PDAC development, so that loss of one could suffice for carcinogenesis. The p16 protein regulates the cell cycle by inhibiting cyclin-dependent kinases (CDK 4,6, and cyklin D). Loss of it leads to uncontrolled cell proliferation through the G1/S checkpoint [21]. On the other hand there is $p19^{ARF}$ whose loss can lead to halting the p53-induced apoptosis and the cell cycle arrest independently of CDKs.

14.1.4.2 *SMAD4*

Another frequently inactivated tumor suppressor is SMAD4. It is a co-transcription factor and a mediator of the TGFβ canonical signaling pathway, which plays important roles in differentiation, tissue homeostasis and cellular growth. As is known of the TGFβ pathway, it has a "dualistic nature" in cancer [19]. In PanIN-1 and PanIN-2 as early phases in clonal expansion, TGFβ signaling is inhibiting the growth of neoplastic cells, but in PanIN-3 and invasive cancer it is tumorigenic. This is due, at least partly, to the loss of SMAD4 along with the canonical arm of the TGFβ pathway. Interestingly, SMAD4 wildtype and its inactivation were found to be associated with different TP53 alterations. Tumors with wildtype SMAD4 had TP53 loss of function alterations, whereas mutant SMAD4 was associated with TP53 gain of function alterations [22]. Those findings need to be put in the clinical context and provide an insight into driver gene mutation interactions or even interdependencies.

The activation of so-called "pro-survival" signaling pathways (e.g. AKT, STAT3, NFκB) in pancreatic carcinomas also causes resistance to apoptosis. At the same time, there are other driver mutations with a lower frequency that increase the heterogeneity of the genetic basis of carcinomas and presumably hinder the efficacy of targeted therapies in pancreatic cancer. Transforming growth factor alpha (TGFα), various fibroblast growth factors, insulin-like growth factor 1 (IGF-1), and hepatocyte growth factor (HGF) are responsible for the formation of the dense extracellular matrix in pancreatic carcinoma by binding to tyrosine kinase receptors (e.g. EGFR) (see below) [23]. The first substance to be approved for molecular targeting was *erlotinib*, an oral EGFR tyrosine kinase inhibitor. In combination with Gemcitabine, at least, a statistical effect was observed with survival prolonged by 2 weeks compared to the Gemcitabine monotherapy [4]. Further targeted therapies with selumetinib, sorafenib, and tipifarnib could not show any clinical benefit so far and were partly even associated with a worse survival compared to gemcitabine monotherapy [4].

14.1.5 Genome Instability and Mutation

There are genetic mutations known to predispose patients carrying them to pancreatic cancer. BRCA2, p16/CDKN2A, STK11, PRSS1, PALP2, FANCC and FANCG and ATM belong to the most important ones. Especially BRCA2 is associated with other malignancies including breast, ovarian and prostate cancer [24]. A recent case-control exome-wide association study to discover germline variants in coding regions also found BRCA2 to have higher rare inactivating variants in PDAC patient's exome compared to healthy controls [25]. Still, familial forms of pancreatic cancer are polygenic according to whole-genome sequencing studies, meaning that kindreds carried one or more germline variant, but the frequency of any one variant never exceeded 3% of the population that was analyzed [19]. Pancreatic tissue is not considered a high proliferative tissue. It is assumed, that the driver gene mutation of sporadic PDAC happens about 20 years before the patient is being diagnosed with the disease. That also explains why patients with inherited high-risk mutations are only about 5 years earlier diagnosed with the disease compared to colon or breast cancer where high risk patients develop familial cancer 10–20 years earlier. As already mentioned, there are four driver genes in PDAC (KRAS, SMAD 4, CDKN2A, TP53) and recent state of the art sequencing technology could not identify more high-frequency genetic targets. This fact also seems to indicate that few evolutionary paths exist to form pancreatic cancer [19].

Recent analysis of whole exome sequencing and copy number variations (CNV) revealed an even more complex picture of the mutational landscape in pancreatic cancer. Beside the aforementioned driver mutations the prevalence of recurrently mutated genes drops to approximately 10% for a small number of genes involved in DNA damage repair, chromatin remodeling or other tumor progression genes. However, a large number of infreque ntly mutated genes dominate the mutation spectrum within pancreatic ductal adenocarcinoma (PDAC) resulting in a significant intertumoral heterogeneity.

Box 14.2 Whole Genome Sequencings
Whole genome sequencing (WGS or full genome sequencing) is the process of determining the complete DNA sequence of an organism's genome at a single time. This entails sequencing all of an organism's chromosomal DNA as well as DNA contained in the mitochondria. WGS should not be confused with methods that sequence specific subsets of the genome - such methods include whole exome sequencing (1–2% of the genome) or SNP (single nucleotide polymorphisms) genotyping (<0.1% of the genome).

14.1.6 Reprogramming of Energy Metabolism and Stroma in Pancreatic Carcinoma

Pancreatic cancer has some special features in its macroscopic and microscopic structure as well as its supply with nutrients. One characteristic feature of pancreatic cancer is a pronounced connective tissue, meaning a large proportion of extracellular matrix which is called desmoplasia. This causes an intratumoral hypoperfusion with low vascularization and correspondingly a hypoxic microenvironment. The extensive extracellular matrix (ECM) as part of the tumor microenviroment (TME) consisting of collagen, fibronectin, proteoglycans (SPARC), and hyaluronic acid is held responsible for the poor chemosensitivity because only a small amount of chemotherapeutic agents can reach the tumor cells [26]. The underlying mechanisms of the stroma enabling neoplastic cells to thrive are of significant clinical interest. It was shown in vitro that inhibition of Hedgehog signaling in gemcitabine resistant mice could increase vascularity and loosen the stroma thus leading to increased gemcitabine concentration in the tumors [27].

14.1.6.1 Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) produce the ingredients of the ECM while themselves predominately originate from pancreatic stellate cells [28]. They were long time considered to only have tumorigenic and pro-metastatic capabilities [29]. But as the understanding of their role within PDAC grew, it became clear that CAFs cells interactions with PDAC cells in the tumor microenvironment can be tumorigenic and inhibitory [30, 31]. Presence or absence of CAFs influences PDAC cancer cell phenotypes. It was shown, that CAFs can contribute to an invasive (by enhancing *eptithelial to mesenchymal transition, EMT*) and a proliferative (PRO) phenotype. Cancer cells can have a double positive phenotype. Through this findings tumor glands were also shown to have an heterogenous architecture concerning expression of EMT and PRO markers that could classify them in various types. Primary tumors are composed of tumor gland "units" that show each various proliferative and metastatic (EMT) capabilities. Different gland types could be linked to

prognosis and neoadjuvant treatment with FOLFIRINOX seems to have an impact on the predominant gland type in resected cancers [32].

Recent research shows that the process of tumor stroma creation is significantly regulated by hyperactivated *fokal adhesion kinase 1* activity. This nonreceptor tyrosine kinase is almost not found in normal pancreatic cells or low grade PanIN lesions whereas it is moderately expressed in high grade PanINs and shows significant upregulation in PDACs. Inhibition of *FAK1* in KPC mice leads to a temporary tumor stasis and prolonged survival of the mice underlining its role as a potential therapy target [33].

The stroma with its consecutive impaired perfusion and tumor specific microenvironment is to a large part considered responsible for the often low response to chemotherapy. Therefore, the stroma has been put into focus in order to improve intratumoral chemotherapy drug concentrations. For the chemotherapeutic agent paclitaxel an improved mechanism of action in individual tumor entities has recently been demonstrated by inclusion in nanoparticle albumin bound (nab: nanoparticle albumin bound). The basis for this is above all improved pharmacokinetics. The albumin carriers allow the cytostatic drug complexes to be bound to so-called SPARC proteins, among others. In healthy tissue SPARC ("secreted protein acidic rich in cysteine") are involved in many biological processes (including wound healing, "tissue remodeling", angiogenesis, etc.) [34, 35]. Gemcitabine seems to increase SPARC expression in a dose-dependent manner. That SPARC increase in the stroma served as a rationale for the use of Nab-paclitaxel in PDAC, because its intratumoral transportation via its albumin binding capabilities seems to be increased. This should lead to the so-called "stromal collapse", the dissolution of parts of the stroma, so that carcinoma cells are brought closer to each other and to blood vessels. In mouse experiments it has been shown that the gemcitabine concentration in the tumor was 2.8 times higher in nab-pacitaxel and gemcitabine treated animals compared to gemcitabine monotherapy [34]. In addition to the known SPARC binding, nab-paclitaxel increases the intratumoral concentration of gemcitabine by inhibiting cytidine deaminase. This enzyme is mainly responsible for the metabolism of gemcitabine [32] . Those findings led to clinical trials involving gemcitabine and nab-paclitaxel by van Hoff et al. showing an increased survival for stage IV PDAC patients from 6.7 to 8.5 months [36, 37].

One component of the ECM is hyaluronic acid, which is a glycoaminoglycan that can bind large amounts of water, thus producing a high interstitial fluid pressure. This pressure leads to vascular collapse, hypoperfusion and hypoxia. The low perfusion due to the dense ECM causing hypoxia, lack of nutrients and low glucose also leads to a high level of metabolic stress and consecutive specific adaptations of the nutrient supply mechanisms in pancreatic carcinoma. Significantly increased glycolysis, autophagy and the increased uptake of serum lipids and proteins via macropinocytosis play a role here. Interestingly, these mechanisms are mainly influenced by *KRAS* [38] and are supposed to happen long before neoplastic cells acquire the stadium of invasion and undergo subclonal evoluation.

In pancreatic carcinoma cells, three "metabolic" subtypes could be detected, the "slow-growing", the "glycolitic" and the "lipogenic" subtypes. Even under *in vitro*

conditions it could be shown that pancreatic carcinoma cells can change their "metabolic subtype" according to the conditions which represents the adaptability, on the other hand clarifies the difficulty of finding appropriate therapies [39]. However, the effects on metabolism in patients with pancreatic carcinoma are also systemically detectable. For example, a newly occurring glucose metabolism disorder or a newly diagnosed diabetes mellitus may indicate pancreatic carcinoma. On the other hand, a longer existing diabetes mellitus, especially in combination with obesity due to increased insulin secretion, is considered a risk factor for tumor development. Systemically, cytokines and proinflammatory mediators presumably produced by pancreatic carcinoma cells and stroma cause a disturbance of metabolism in muscle, liver and fatty tissue leading to tumor cachexia. Increased muscle degradation leads to the release of branched-chain amino acids which are used to supply the PDAC with nutrients and some of which can already be detected before the clinically manifest cachexia [40].

14.1.7 Metastasis of Pancreatic Cancer

Approximately 40% of the patients show distant metastasis upon diagnosis [41]. Metastasis formation has not been fully understood yet. Even though controversially discussed in recent years, epithelial to mesenchymal transformation (EMT) seems to play an important role in metastasis of PDAC [42–44]. EMT describes the transition from an epithelial to a mesenchymal phenotype [45]. Its regulation is complex and so called EMT-inducing transcription factors (EMT-TF) such as SNAIL (Zinc finger protein SNAIL), ZEB (Zinc finger E-boxbinding homeobox 1), and Twist (Twist Basic Helix-LoopHelix Transcription Factor 1) play crucial roles. Even though the role of SNAIL and Twist in metastasis was questioned, Krebs and colleagues could show that depletion of ZEB1 in KPC mice significantly reduced metastasis during PDAC progression [46]. Furthermore, miRNAs miR-200 and miR-34 regulate EMT via a negative feedback loop to maintain epithelial and mesenchymal homeostasis [45, 47]. The EMT process is considered partially reversible. During the EMT process intermediate stages are meta-stable and enhance intravasation and consecutively provide a step towards metastasis [45].

Circulating tumor cells (CTCs) present in the majority with intermediate stages of EMT in favor of mesenchymal characteristics which allow for high cellular motility [45, 48]. For the colonization of other organs the reverse process of EMT (called MET) needs to be activated in PDAC cells. So far it is assumed that only the epithelial stages of PDAC cells can extravasate and embed in other tissues to form metastases [28, 49]. Therefore, the plasticity of carcinoma cells plays a very important role in the process of metastasis. It has as well been suggested that EMT enhances tumor resistance to chemotherapy, because its suppression *in vitro* promoted expression of nucleoside transporters which consecutively increased gemcitabine sensitivity in mice [42]. One major driver for EMT initiation is TGFβ

[48, 50]. Still, many details of the EMT/MET process are under investigation and have not been fully understood.

Whole genome sequencing provided further insight into the mutational properties of primary tumors and metastases. Interestingly, analyses comparing the mutational status of driver genes in PDAC primary and metastases have shown identical mutations in all studied lesions. Furthermore, even the mutations in passenger genes showed a greater similarity than they did when comparing two normal pancreatic cells [51]. Knowing that driver gene mutations are consistent in primary and metastases in an individual patient is of great clinical significance as it may enhance success of targeted therapies. On the other hand, instead of genomic alterations, epigenetic alterations seem to enhance metastasis decisively. One explanation was provided by the identification of large-scale losses of heterochromatin marks, among others methylation of H3K9 and H4K20 histones, and DNA methylation [22, 51]. Besides abovementioned mechanisms there are many other possible programs that contribute to metastasis such as reactivation of embryonic programs, the generation of a premetastatic niche in target organs, and changes in metabolism pathways [28].

14.2 Conclusions

The understanding of pancreatic cancer has evolved significantly over the last two decades. On the basis of genomic analyses hallmarks of cancer as defined for all cancer entities can be defined for PDAC as well. Methods allowing for in depth analysis of PDAC genomic analysis and single cell expressions patterns of relevant markers contribute to dissect the diseases complexity and will allow for individualized therapeutic approaches in the future.

References

1. Wang L, Xie D, Wei D, Su GH. Pancreatic acinar-to-ductal metaplasia and pancreatic cancer. New York: Springer; 2019. https://doi.org/10.1007/978-1-4939-8879-2_26.
2. Basturk O, et al. A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol. 2015;39:1730–41.
3. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378:607–20.
4. Tanaka S. Molecular pathogenesis and targeted therapy of pancreatic cancer. Ann Surg Oncol. 2016;23:197–205.
5. Ott C, Heinmöller E, Gaumann A, Schölmerich J, Klebl F. Intraepitheliale Neoplasien (PanIN) und intraduktale papillär-muzinöse Neoplasien (IPMN) des Pankreas als Vorläufer des Pankreaskarzinoms. Med Klin. 2007;102:127–35.
6. Mateos RS, Conlon KC. Pancreatic cancer. Surgery (Oxford). 2016;34:282–91.

7. Jones S, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
8. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388:73–85.
9. Notta F, et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. Nature. 2016;538:378–82.
10. Zhang C-Z, et al. Chromothripsis from DNA damage in micronuclei. Nature. 2015;522:179–84.
11. Real FX. A "catastrophic hypothesis" for pancreas cancer progression1 1The author thanks J. Alguacil, D. Longnecker, N. Malats, X. Mayol, M. Porta, and A. Sodhi for valuable comments and suggestions to a prior version of this manuscript, as well as for many stimulating discussions and J. Franquesa for the artwork. Gastroenterology. 2003;124:1958–64.
12. Mueller S, et al. Evolutionary routes and KRAS dosage define pancreatic cancer phenotypes. Nature. 2018;554:62–8.
13. Real FX, de Andrés MP. Mutant Kras dosage and chromothripsis: the right ingredients for a pancreatic cancer catastrophe. Trends Cancer. 2018;4:399–401.
14. Lennon AM, et al. The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia? Cancer Res. 2014;74:3381–9.
15. Waddell N, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518:495–501.
16. Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1199–1209.e4.
17. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011;144:646–74.
18. Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene. 2005;24:2899–908.
19. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer. 2016;16:553–65.
20. Mello SS, et al. A p53 super-tumor suppressor reveals a tumor suppressive p53-Ptpn14-Yap axis in pancreatic cancer. Cancer Cell. 2017;32:460–473.e6.
21. Ansari D, Gustafsson A, Andersson R. Update on the management of pancreatic cancer: surgery is not enough. World J Gastroenterol. 2015;21:3157–65.
22. Pickup M, Novitskiy S, Moses HL. The roles of TGFβ in the tumour microenvironment. Nat Rev Cancer. 2013;13:788–99.
23. Yachida S, et al. Clinical significance of the genetic landscape of pancreatic cancer and implications for identification of potential long-term survivors. Clin Cancer Res. 2012;18:6339–47.
24. Iacobuzio-Donahue CA, Velculescu VE, Wolfgang CL, Hruban RH. Genetic basis of pancreas cancer development and progression: insights from whole-exome and whole-genome sequencing. Clin Cancer Res. 2012;18:4257–65.
25. Grant RC, et al. Exome-wide association study of pancreatic cancer risk. Gastroenterology. 2018;154:719–722.e3.
26. Feig C, et al. The pancreas cancer microenvironment. Clin Cancer Res. 2012;18:4266–76.
27. Yao D, Dai C, Peng S. Mechanism of the mesenchymal–epithelial transition and its relationship with metastatic tumor formation. Mol Cancer Res. 2011;9:1608–20.
28. Olive KP, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009;324:1457–61.
29. David CJ, et al. TGF-β tumor suppression through a lethal EMT. Cell. 2016;164:1015–30.
30. Makohon-Moore AP, et al. Limited heterogeneity of known driver gene mutations among the metastases of individual patients with pancreatic cancer. Nat Genet. 2017;49:358–66.
31. Vakoc CR, Tuveson DA. Untangling the genetics from the epigenetics in pancreatic cancer metastasis. Nat Genet. 2017;49:323–4.
32. Ligorio M, et al. Stromal microenvironment shapes the intratumoral architecture of pancreatic cancer. Cell. 2019;178:160–175.e27.

33. Orth M, et al. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol. 2019;14(1):141.
34. Kleeff J, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
35. Gore J, Korc M. Pancreatic cancer stroma: friend or foe? Cancer Cell. 2014;25:711–2.
36. Jiang H, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat Med. 2016;22(8):851–60.
37. Neuzillet C, et al. Stromal expression of SPARC in pancreatic adenocarcinoma. Cancer Metast Rev. 2013;32:585–602.
38. Vaz J, Ansari D, Sasor A, Andersson R. SPARC. Pancreas. 2015;44:1024–35.
39. Frese KK, et al. nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discov. 2012;2:260–9.
40. Goldstein D, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst. 2015;107:dju413.
41. Hoff DDV, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
42. Ryan DP, Hong TS, Bardeesy N. Pancreatic Adenocarcinoma. N Engl J Med. 2014;371:1039–49.
43. Choe JH, et al. Emerging therapeutic targets in pancreatic adenocarcinoma. New York: Springer; 2018. https://doi.org/10.1007/978-1-4939-7193-0_92.
44. Perera RM, Bardeesy N. Pancreatic cancer metabolism: breaking it down to build it Back up. Cancer Discov. 2015;5:1247–61.
45. Konstantinidis IT, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a 'true' R0 resection? Ann Surg. 2013;257:731–6.
46. Zheng X, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature. 2015;527:525–30.
47. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119:1420–8.
48. Rhim AD, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148:349–61.
49. Nieto MA, Huang RY-J, Jackson RA, Thiery JP. EMT: 2016. Cell. 2016;166:21–45.
50. Krebs AM, et al. The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol. 2017;19:518–29.
51. Wang S, Huang S, Sun YL. Epithelial-mesenchymal transition in pancreatic cancer: a review. Biomed Res Int. 2017;2017:1–10.

Chapter 15
Pathobiology of Precursors to Pancreatic Cancer

Georg Oberhuber

Take Home Messages

- Pancreatic precursors are visible (e.g. cystic lesions) or invisible (pancreatic intraepithelial neoplasia, PanIN).
- The risk of malignant degeneration is depending on type and/or location of the pancreatic precursor.
- The exact classification of the precursor type is dependent on histology with or without immunohistology.
- The various pancreatic precursors have different molecular pathways.

Pearls and Pitfalls

- Intraductal and cystic pancreatic neoplasms now have a 2-tier grading system of low-grade and high-grade dysplasia.
- Although most IPMN follow a benign clinical course they may develop high grade dysplasia or become malignant.
- KRAS mutations are considered early molecular events in PanIN, IPMN and MCN.
- The molecular pathway of ITPN and IOPN carcinogenesis is different.
- GNAS mutations are together with RNF43 mutations relatively specific molecular alteration in IPMN.

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Future Perspectives
- Improvement in bioinformatics may allow for a more comprehensive analysis of whole exome genomic data to understand precursors.
- Detailed studies of epigenetic events in pancreatic cancerogenesis are needed.
- Data on proteomics to further refine the knowledge on PDAC development is needed.
- The role of microRNA in PDAC cancerogenesis needs to be better understood.
- Understanding the "point of no return" alterations in pancreatic precursors would be essential for developing clinical decision tools.

15.1 Introduction

The classification of pancreatic neoplasms is based on the lines of cellular differentiation that they display (ductal, acinar, neuroendocrine, others) and on their gross configuration (intraductal, cystic, solid). Cystic and intraductal neoplasms make up 4–5% of pancreatic neoplasms and include the true cystic neoplasms such as IPMN, mucinous cystic and serous cystic neoplasms as well as those with degenerative cystic changes which can occur in any typically solid neoplasm such as pancreatic duct adenocarcinoma (PDAC) and neuroendocrine tumors.

This chapter will focus on intraductal (preinvasive) tumors and cysts of the pancreatic gland. The most important lesions of this group are pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). As other precursor lesions have comparable and important knowledge to present concerning malignant transformation, other lesions such as mucinous cystic neoplasm (MCN) and intraductal tubulopapillary neoplasm (ITPN) will be presented as well. Acinar cell cystadenoma and serous cystadenoma are not discussed in this chapter.

15.1.1 Pancreatic Intraepithelial Neoplasia (PanIN)

PanINs are microscopic non-invasive, flat or micropapillary epithelial neoplasms confined to the pancreatic ducts. They occur both in the main pancreatic duct and in the ducts of peripheral pancreatic lobules. PanIN is often multifocal and may show different grades of dysplasia in the same pancreas. In the current fifth edition of the WHO Classification of Digestive System Tumours the former three-tiered grading system has been replaced by a two-tiered system [1], as proposed in the Baltimore consensus meeting [2]. Low grade PanIN includes the former PanIN-1 and PanIN-2, whereas high grade PanIN includes the former PanIN-3. Low grade PanIN is commonly found in the general population as observed in autopsy [3] and resection specimen studies, in particular in patients older than 40 years [4], and is therefore of no clinical relevance. In contrast, high grade PanIN is frequently observed in patients with familial predisposition to PDAC [5] and in pancreata with PDAC [6]. Indeed, the majority of PDACs are thought to arise from high grade PanINs [2]. In

the UICC staging system (TNM) high grade PanIN is categorized as cancer in situ (Tis) thus highlighting its clinical significance.

Histologically, low grade PanIN is composed of cuboidal to columnar cells producing various amounts of mucin (Fig. 15.1). These lesions are flat or papillary and show mild to moderate atypia. Known histological variants are the intestinal type with goblet cells, the foamy cell type and the oncocytic type. High grade PanIN is typically micropapillary or papillary and shows high grade atypia (Fig. 15.1). As already pointed out, it is currently believed, that most pancreatic cancers derive from non-invasive precursors, in the majority of cases from PanIN and IPMN. Histologic progression is mirrored by genetic progression, including copy number alterations or a trend towards a higher degree of clonality for any individual molecular aberration. Also somatic mutations in key driver genes accumulate which finally results in the development of invasive carcinoma (Fig. 15.2).

In PanIN, telomere shortening, which may lead to chromosomal instabilities, and somatic point mutation of KRAS are among the first to occur. KRAS mutations have a prevalence of greater than 90% (even in low-grade PanIN lesions). Mutations in KRAS are activating mutations and almost always occur at specific hotspot positions (codons 12, 13, 61) [7]. The KRAS encoded protein is in a central position of the MAPK (microtubule associated protein kinase) pathway, an important

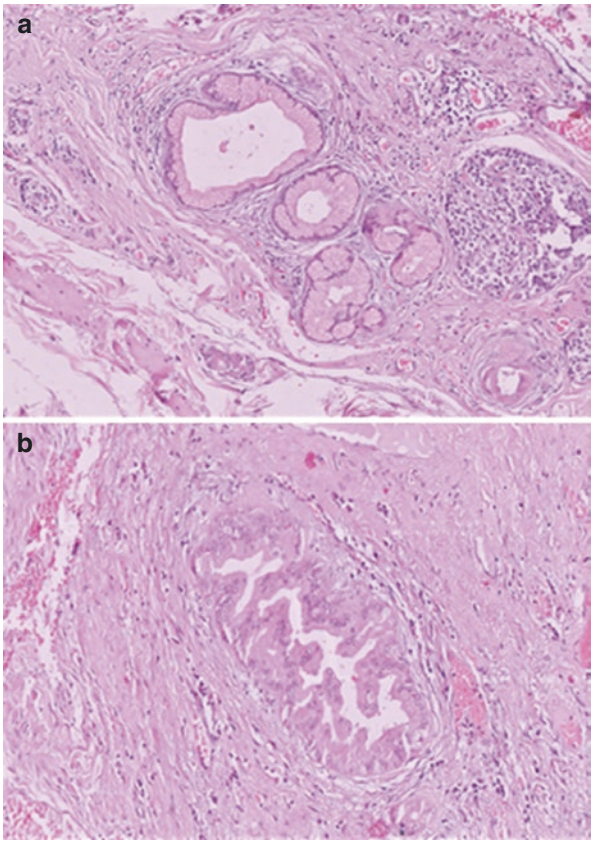

Fig. 15.1 Pancreatic intraepithelial neoplasia (PanIN). (**a**) Low grade PanIN. The epithelial cells show gastric differentiation. Hematoxylin and eosin. (**b**) High grade PanIN. The epithelial cells are papillary and show high grade dysplasia. Hematoxylin and eosin

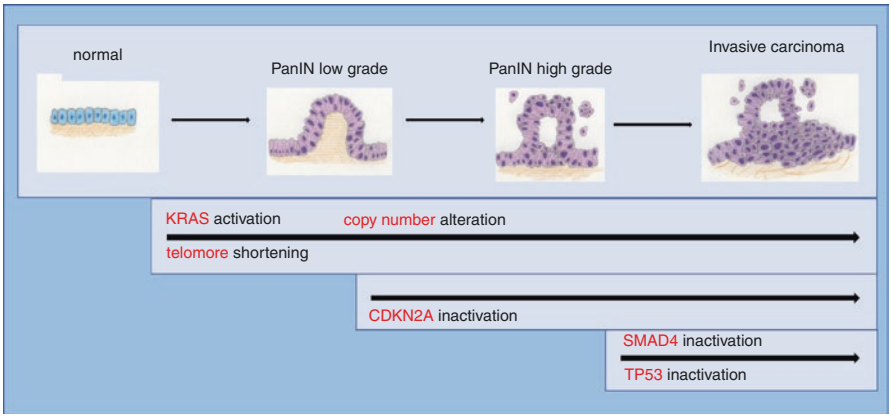

Fig. 15.2 The PanIN model. This is a schematic drawing of the molecular events occurring in the classical pathway of pancreatic cancer development. (Drawings by Monika Oberhuber)

pathway for the induction of cell proliferation and differentiation. As a consequence, the effected cells have a survival advantage thus increasing the possibility that further alterations of their genome may develop. Furthermore, it may be an explanation for the development of the mild folding of the epithelium in more progressed low grade PanIN, which is in contrast to unaffected normal ducts that are lined by flat epithelium. Disease progression to high grade PanIN is associated with wide-spread clonal copy-number alterations (i.e. somatic changes to chromosome structure that results in gain or loss of copies of sections of DNA). Furthermore, the loss of CDKN2A (p16) expression is a second central event in pancreatic carcinogenesis. It typically occurs after KRAS mutation and is more prevalent in high grade PanIN when compared to low grade PanIN [8]. CDKN2A protein acts as an important regulator of cell proliferation by blocking phosphorylation of RB, which inhibits passage through the G1/S cell cycle checkpoint, e.g. when DNA damage occurs or when cells are exposed to hyperproliferative signals. Homozygous deletion, intragenic mutation coupled with loss of the second allele, and epigenetic silencing by promoter hypermethylation are molecular mechanisms leading to CDKN2A loss. Histologically these molecular changes are accompanied by the development of a complex architecture and high-grade atypia.

Mutations in TP53 and SMAD4/DPC occur late and are considered to drive invasiveness [9, 10].

In conventional histology cancerization of pancreatic ducts, i.e. spreading of PDAC along preexisting pancreatic ducts and ductules, can mimic high-grade PanIN [11]. In contrast to PanIN, cancerization of pancreatic ducts will frequently show an abrupt transition between the marked dysplasia of the neoplastic cells and the complete absence of dysplasia in the normal duct epithelium. Furthermore, the observation of TP53 and SMAD4 mutations in such a lesion favor cancerization of pancreatic ducts [9].

15.1.2 Acinar-Ductal Metaplasia (ADM)

Another potential precursor lesion is acinar-ductal metaplasia (ADM) [12]. Currently, however, its biological significance in human pancreas is still unclear. ADM develops in pancreatic acini and is characterized by tubular complexes showing loss of acinar markers and progressive expression of ductal markers. It is associated with inflammation and fibrosis.

Box 15.1 Definitions of PanIN Lesions

- PanINs are microscopic non-invasive epithelial neoplasms confined to the pancreatic ducts.
- PanIns may be of low grade or of high grade
- The prevalence of KRAS mutations in PanIN is greater than 90%
- Cancerization of pancreatic ducts may mimic the appearance of high grade PanIN

15.1.3 Intraductal Papillary Mucinous Neoplasm (IPMN)

IPMNs [13] are intraductal precursor lesions that constitute 60% of cyst-forming neoplasms of the pancreas. They show similar cytological changes when compared to PanIN with the main difference between these two entities being size. PanINs are usually defined as lesions with a ductal diameter >0.5 cm, whereas ducts of IPMNs hold >0.5 cm and are in contrast to PanINs grossly visible.

The majority of IPMN occurs in the pancreatic head and a large proportion of IPMNs involves only one portion of the pancreatic duct. However, IPMNs may be multifocal in up to 40% [13] or may involve the whole pancreatic duct. The average age of presentation is >60 years and a prevalence rising to 6.7% in people in their eighth decade of life [14]. The 5-year survival rate is 85–100%. When an invasive tumor develops the 5-year survival rate drops to 34–62% [15] with some authors reporting a better survival when compared to conventional PDAC [16] and others finding a better survival only in the colloid and oncocytic subtypes [17]. Those with an invasion <5 mm have an excellent prognosis [18].

With the aid of imaging studies or histology IPMNs are classified into three types, depending on the type of duct involved: main duct (MD) IPMN, branch duct (BD) IPMN and mixed type (Fig. 15.3). In imaging studies MD-IPMN is characterized by a diffuse or segmental dilatation of the main pancreatic duct (MPD) of >0.5 cm without other causes of obstruction. Pancreatic cysts of >0.5 cm that communicate with the MPD are designated BD- IPMN. Mixed type IPMN meets the criteria of both MD-IPMN and BD-IPMN. One problem with this definition is that the correlation between histologic and imaging classification of IPMN type is only 70% [19, 20]. E.g. in imaging studies, a histologically involved MPD may appear

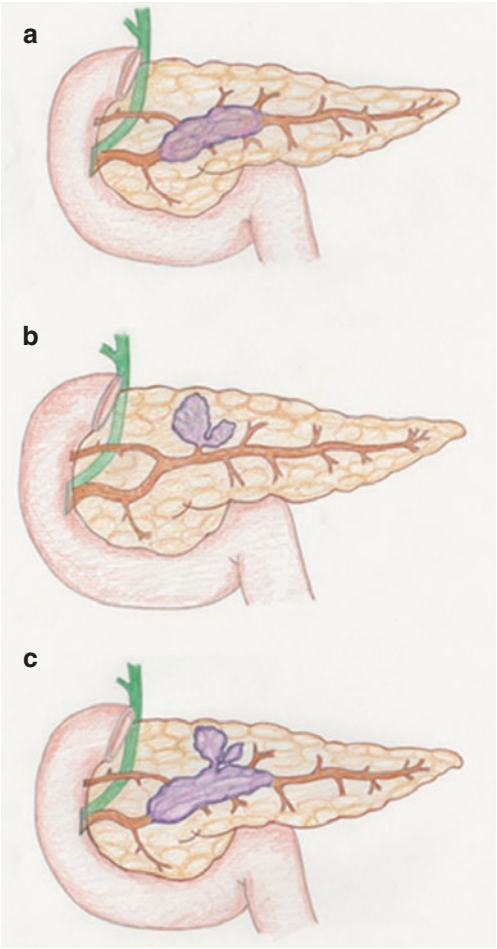

Fig. 15.3 The three types of intraductal papillary mucinous neoplasia (IPMN). (**a**) Main duct IPMN. (**b**) Branch duct IPMN. (**c**) Mixed type IPMN. (Drawings by Monika Oberhuber)

normal, when it is not dilatated. On the other hand, BD-IPMN may lead to dilatation of the MPD through ductal hypertension induced by pancreatitis, mucin or protein plugs. Despite these shortcomings in a few patients, management of patients with IPMN is based on the results of imaging studies.

15.1.4 Histology of IPMN

IPMN has a flat or papillary mucinous epithelium and a dense fibrotic wall without ovarian like stroma. The papillae range in size from flat to grossly visible. In parallel to the situation in PanIN a 2-tier grading system with low grade and high grade IPMN is applied [2]. Three histological types are observed: the gastric, the intestinal and the pancreaticobiliary type.

The vast majority (~70%) of IPMN is of gastric type (Fig. 15.4). The gastric type usually occurs in branch ducts and is usually low-grade [21]. Rarely, adenoma like structures may develop that resemble pyloric gland adenomas. Reported cases with pyloric gland adenoma like structures mainly developed in the MD, were of low grade and showed a favorable clinical course. They are best diagnosed as IPMN of gastric type, pyloric gland variant [22]. Only a small percentage of gastric type IPMN develops into carcinoma of tubular type, i.e. conventional PDAC.

The intestinal type (Fig. 15.4) is the second most common type and is found in ~20% of IPMNs. Typically, it occurs in the main duct. This type usually reveals high grade dysplasia [21].

The pancreaticobiliary type (Fig. 15.4) is the least common. It typically involves the main duct and is often high grade [23].

Previous studies identified six crucial driver genes in pancreatic ductal neoplasia, namely *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, shared in PDACs and IPMNs, as well as *GNAS* and *RNF43* in the IPMN pathway specifically [7, 24, 25] (Fig. 15.5). CDKN2A, TP53, SMAD4 and RNF43 are tumor suppressor genes that undergo inactivating mutations, whereas KRAS and GNAS undergo activating mutations.

KRAS and GNAS are likely to be the earliest genetic alterations in IPMN and are together with RNF43 mutations relatively specific molecular alteration in IPMNs [24, 25]. In contrast to PanIN SMAD4 mutations are uncommon in IPMN and are mainly observed in IPMN associated carcinomas. Recent studies show that driver gene heterogeneity [26] is prevalent in IPMN with KRAS and GNAS mutations being more heterogenous in low grade dysplasia with respect to high grade

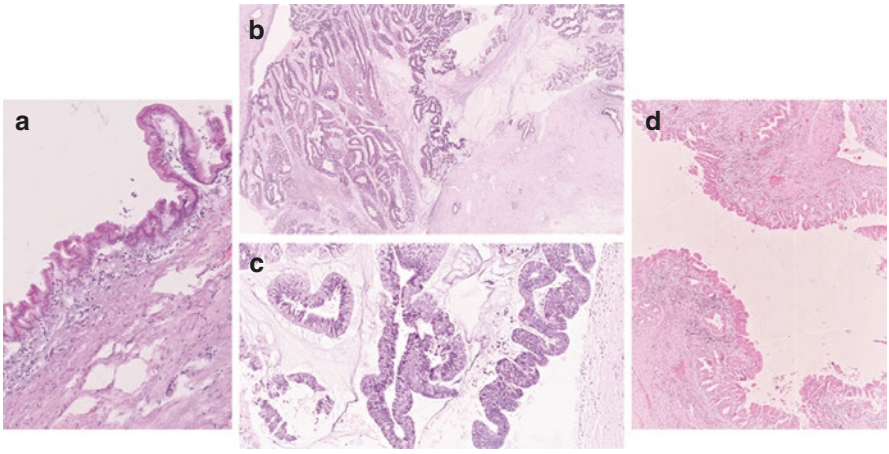

Fig. 15.4 Histological IPMN types. (**a**) Low grade IPMN of gastric type. The epithelial cells show a micropapillary architecture and resemble gastric epithelial cells. Hematoxylin and eosin. (**b**) High grade IPMN of intestinal type. The tumor is forming an intraductal nodule which was considered an high risk stigma in imaging studies. Hematoxylin and eosin. (**c**) High power view of the high grade IPMN of intestinal type depicts significant epithelial dysplasia. Hematoxylin and eosin. (**d**) High grade IPMN of pancreaticobiliary type. The epithelial lining is characterized by a micropapillary architecture and high grade dysplasia. Hematoxylin and eosin

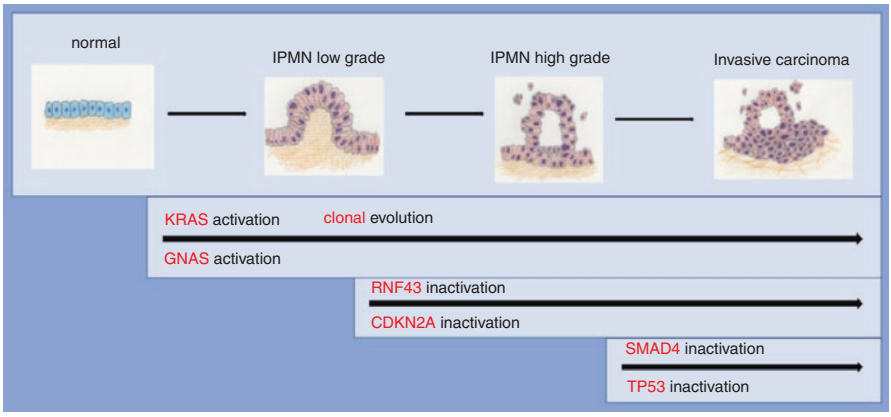

Fig. 15.5 IPMN Pathway. This is a schematic drawing of the molecular events occurring in the IPMN pathway of pancreatic cancer development. (Drawings by Monika Oberhuber)

dysplasia [27]. After fixation of early driver mutations, there is a convergent evolution of mutations in later driver genes such as RNF43 (encoding an E3 ubiquitin ligase), CDKN2A and TP53 finally leading to the development of PDAC.

15.1.5 Invasive Carcinomas in IPMN

IPMN is often co-located in the pancreas when a PDAC is present, yet it is often unclear whether the invasive carcinoma arose from the IPMN or whether they coexist and evolved in parallel. If the carcinoma arises in the area of IPMN it is designated IPMN with associated invasive carcinoma. If the carcinoma is not continuous with IPMN, it is designated IPMN with concomitant invasive carcinoma. Two types of invasive carcinoma, namely colloidal and tubular (conventional) carcinoma, may develop from IPMN with colloid carcinoma showing a better prognosis. Colloid carcinomas develop from intestinal type IPMN and show an 'intestinal' differentiation with production of extracellular mucin and expression of the immunohistological markers CDX2 and MUC2. In contrast, tubular carcinomas are similar to conventional PDAC.

15.1.6 Cytology of Cystic Lesions in the Pancreas

Only in centers with expertise in EUS-FNA and interpretation of cytological findings cytology may be of additional value, in particular in evaluating small BD-IPMN without worrisome features. However, its sensitivity is limited by the scant cellularity. Finding cells with significant cellular atypia in the cystic fluid is a sensitive predictor of carcinoma or high-grade dysplasia.

Furthermore, molecular analysis of cystic fluid is still evolving. While KRAS mutations are good predictors of mucinous cysts but not necessarily malignancy, GNAS mutations may be helpful in distinguishing significant mucinous cysts from indolent cysts. Currently novel methylated DNA markers (MDMs) that discriminate HGD/PC from low-grade dysplasia or no dysplasia are validated [28].

Box 15.2 Comparing Features of PanIN and IPMN

- The histologic appearance of PanIN and IPMN is similar. IPMN are defined by a size of >0.5 cm and gross visibility
- Three histological types are observed: the gastric, the intestinal and the pancreaticobiliary type.
- With the aid of imaging studies or histology IPMNs are classified into main duct (MD) IPMN, branch duct (BD) IPMN and mixed type.
- Findings on imaging studies called "worrisome features" and "high risk stigmata" are applied to assess the risk of HGD or carcinoma in an IPMN

15.1.7 Pancreatic Intraductal Oncocytic Papillary Neoplasm (IOPN)

The intraductal oncocytic papillary neoplasm [29] accounts for 4.5% of all intraductal neoplasms. Patients are 20–80 years old (average 60 years) with an equal distribution among the sexes. Approximately 70% of IOPN occur in the pancreatic head and involve the main duct. 10% diffusely involve the gland.

Grossly, IOPN may be unilocular or multilocular and cystic with an average size range of 4–6 cm. They typically form tan-brown, friable papillary projections. Histologically it is characterized by oncocytic cells (Fig. 15.6) with abundant granular and eosinophilic cytoplasm [30] developing complex arborizing papillae with delicate cores or solid nodules in cystically dilated pancreatic ducts. Characteristically tumor cells are MUC1 and MUC6 positive.

IOPN are often classified as high grade and they develop invasive carcinoma in 25–50%, which is, however, often minimally invasive.

IOPN typically lack alterations in KRAS, GNAS and RNF43 indicating their difference to IPMN. Recently, IOPNs were found to have recurring fusions resulting in increased protein kinase A (PKA) activity by activating the PRKACA or PRKACB genes. Specifically fusions of ATP1B1–PRKACB, DNAJB1–PRKACA, or ATP1B1–PRKACA were observed [31]. Interestingly, the DNAJB1–PRKACA fusion was also observed in fibrolamellar hepatocellular carcinoma, an oncocytic neoplasm of the liver [32]. Other genes recurrently mutated in IOPN include ARHGAP26, ASXL1, EPHA8 and ERBB4 [30].

Box 15.3 Intraductal Oncocytic Papillary Neoplasm

- IOPN is characterized by oncocytic cells with abundant granular and eosinophilic cytoplasm
- Their molecular profile is different from PanIN and IPMN
- IOPN have an excellent prognosis after surgical resection

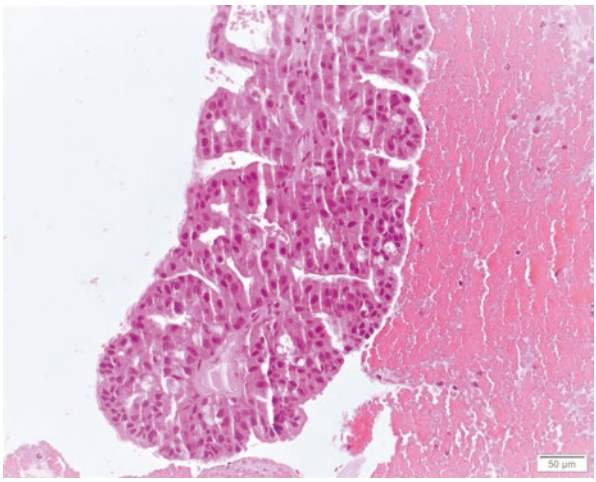

Fig. 15.6 IOPN. Cytologic specimen of an IOPN with its characteristic epithelial cells with their broad eosinophilic cytoplasm. (Courtesy of Irene Esposito). Hematoxylin and eosin

15.1.8 Intraductal Tubulopapillary Neoplasm (ITPN)

Yamaguchi et al. were the first ones to describe ten cases of that previously undefined type of tumor [33]. ITPN is an intraductal predominantly tubule-forming neoplasm with high grade dysplasia and ductal differentiation without overt production of mucin. It is a rare tumor and accounts for less than 1% of exocrine pancreatic neoplasms and 3% of all intraductal neoplasms of the pancreas. The average age range of patients is 59 years. About half of all ITPN occur in the pancreatic head and a third involve the gland diffusely. The average size is 4.5 cm.

ITPN is a solidly appearing epithelial neoplasm obstructing the main pancreatic duct thereby causing upstream duct dilation. It is composed of back-to-back tubular glands and less often papillae (Fig. 15.7). An invasive component develops in 70% of cases. Histologically, the carcinoma may appear similar to the intraductal component. If this is the case, it is often difficult to establish whether invasive carcinoma is present. In the remainder carcinomas developing from ITPN are highly infiltrative and then are readily recognized as malignant.

ITPN lacks gastroenteric differentiation and MUC 5AC, a marker of all types of IPMN, is almost never expressed in ITPN. Signs of pancreatic duct differentiation

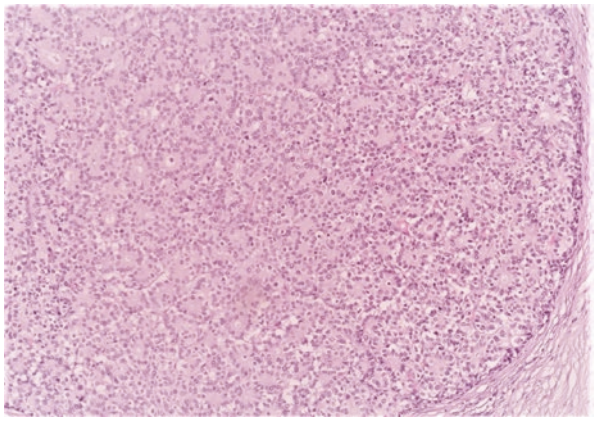

Fig. 15.7 ITPN. ITPN with epithelial cells showing tubular conformation. Hematoxylin and eosin

are revealed by expression of CK7 and/or CK19, as well as focal MUC1 and variable MUC6 [34] expression.

ITPN may be difficult to distinguish from acinar cell carcinoma which may also show intraductal growth. Acinar cell carcinomas may be recognized by labelling with marker of pancreatic exocrine enzymes, such as trypsin.

ITPN have distinct genetic alterations [35]. The following genes may be involved: CDKN2A, certain chromatin remodeling genes (MLL1, MLL2, MLL3, BAP1, PBRM1, EED, and ATRX), phosphatidylinositol 3-kinase (PI3K) pathway (PIK3CA, PIK3CB, INPP4A, and PTEN), FGFR2 fusions (FGFR2-CEP55, FGFR2-SASS6, DISP1-FGFR2, FGFR2-TXLNA, and FGFR2-VCL) and STRN-ALK fusion.

Box 15.4 Intraductal Tubulopapillary Neoplasm (ITPN)

- ITPN is a rare intraductal predominantly tubule-forming neoplasm with high grade dysplasia and ductal differentiation.
- Carcinoma may develop in ITPN and may appear similar to the intraductal component.
- Noninvasive ITPN has a good prognosis

15.1.9 Mucinous Cystic Neoplasm (MCN)

This is a non-invasive mainly solitary cystic neoplasm composed of mucin-producing cells associated with typical subepithelial ovarian type stroma. It comprises about 8% of the cystic lesions of the pancreas with an average age of the patients of 48 years. MCN is predominantly found in female patients with >98%

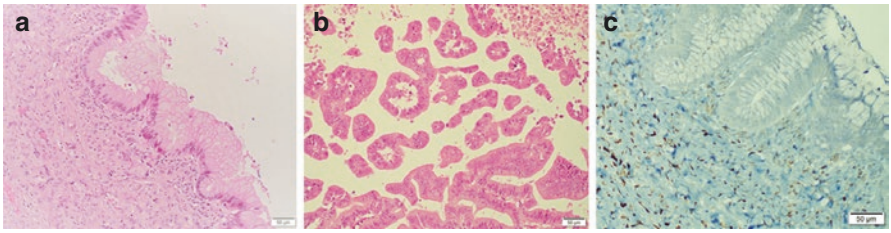

Fig. 15.8 MCN. (**a**) Low grade MCN. The epithelial cells show well developed epithelial cells with basal small nuclei. (Courtesy of Irene Esposito). Hematoxylin and eosin. (**b**) High grade MCN. This high grade MCN shows a complex architecture in combination with an epithelial lining with highly atypical cells. (Courtesy of Irene Esposito). Hematoxylin and eosin. (**c**) MCN stroma. MCN with its typical ovarian like stroma, imunohistologically highlighted by progesterone positive nuclei (in brown). (Courtesy of Irene Esposito)

occurring in the body or tail of the pancreas. In contrast to IPMN main pancreatic and large interlobular ducts do not communicate with cysts in the majority of cases. Clinically, usually a solitary large cyst with a mean diameter of 7–10 cm is observed. Larger tumors may produce symptoms due to compression of adjacent structures, whereas tumors <3 cm are typically found incidentally.

Grossly MCN has a thick wall and is filled with thick tenacious mucoid material. Histologically the tumor cells are tall columnar mucin producing epithelial cells with either low or high grade dysplasia (Fig. 15.8). The ovarian type stroma in the cyst wall is required for the diagnosis. The stroma is often estrogen and/or progesterone receptor positive (Fig. 15.8) and may stain with antibodies against inhibin.

The origin of this ovarian type stroma is not clear. It is conceivable that ectopic ovarian stroma incorporated during embryogenesis in the pancreas and other organs may become activated in the setting of a hormonal imbalance, releasing hormones and growth factors and causing nearby epithelium to proliferate and form cystic neoplasms.

Molecularly, MCNs resemble IPMNs, except that unlike IPMNs, MCNs do not typically harbor GNAS alterations. Whole exome sequencing of 8 MCNs identified KRAS (75%), RNF43 (50%) and TP53 (25%) as highly prevalent events in these lesions [36]. KRAS mutation is found in a third of low-grade and in 90% of high grade MCN. TP53 mutation and SMAD4 loss is usually found in advanced MCN with an invasive component.

Box 15.5 Mucinous Cystic Neoplasm (MCN)

- MCN is a mainly solitary cystic neoplasm composed of mucin-producing cells associated with typical subepithelial ovarian type stroma.
- MCN is predominantly found in female patients with >98% occurring in the body or tail of the pancreas.
- Intracystic papillary excrescences and/or mural nodules, tumor size >5 cm and CA19.9 levels >37 kU/L are suggestive of high-grade dysplasia or invasion.

15.2 Conclusions

PanIN and IPMN are the prevailing precursors of PDAC. MCN, and in particular IOPN and ITPN are rare tumours and therefore are of minor importance in pancreatic cancer genesis. The precursor lesions differ in their macroscopic and/or histologic presentation. Molecularly, somatic KRAS point mutations with gain of function play a central role in PanIN, IPMN and MCN. The molecular pathways of ITPN and MCN are more complex and differ from the above-mentioned classical pathways.

References

1. Basturk O, Esposito I, Fukushima N, Furukawa T, Hong SM, Klöppel G, Maitra A, Zamboni G. Pancreatic intraepithelial neoplasia. In: Digestive system tumours. 5th ed. Lyon: International Agency of Research on Cancer. p. 307–9.
2. Basturk O, Hong S-M, Wood LD, et al. A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol. 2015;39:1730–41.
3. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol. 1984;15:677–83.
4. Lüttges J, Reinecke-Lüthge A, Möllmann B, Menke MA, Clemens A, Klimpfinger M, Sipos B, Klöppel G. Duct changes and K-ras mutations in the disease-free pancreas: analysis of type, age relation and spatial distribution. Virchows Arch Int J Pathol. 1999;435:461–8.
5. Shi C, Klein AP, Goggins M, Maitra A, Canto M, Ali S, Schulick R, Palmisano E, Hruban RH. Increased prevalence of precursor lesions in familial pancreatic cancer patients. Clin Cancer Res. 2009;15:7737–43.
6. Andea A, Sarkar F, Adsay VN. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. Mod Pathol. 2003;16:996–1006.
7. Felsenstein M, Hruban RH, Wood LD. New developments in the molecular mechanisms of pancreatic tumorigenesis. Adv Anat Pathol. 2018;25:131–42.
8. Furukawa T, Fujisaki R, Yoshida Y, Kanai N, Sunamura M, Abe T, Takeda K, Matsuno S, Horii A. Distinct progression pathways involving the dysfunction of DUSP6/MKP-3 in pancreatic intraepithelial neoplasia and intraductal papillary-mucinous neoplasms of the pancreas. Mod Pathol. 2005;18:1034–42.
9. Hosoda W, Chianchiano P, Griffin JF, et al. Genetic analyses of isolated high-grade pancreatic intraepithelial neoplasia (HG-PanIN) reveal paucity of alterations in TP53 and SMAD4. J Pathol. 2017;242:16–23.
10. Hata T, Suenaga M, Marchionni L, Macgregor-Das A, Yu J, Shindo K, Tamura K, Hruban RH, Goggins M. Genome-wide somatic copy number alterations and mutations in high-grade pancreatic intraepithelial neoplasia. Am J Pathol. 2018;188:1723–33.
11. Hutchings D, Waters KM, Weiss MJ, Wolfgang CL, Makary MA, He J, Cameron JL, Wood LD, Hruban RH. Cancerization of the pancreatic ducts. Am J Surg Pathol. 2018;42:1556–61.
12. Esposito I, Seiler C, Bergmann F, Kleeff J, Friess H, Schirmacher P. Hypothetical progression model of pancreatic cancer with origin in the centroacinar-acinar compartment. Pancreas. 2007;35:212–7.

13. Basturk O, Esposito I, Fukushima N, Furukawa T, Hong SM, Klöppel G, Maitra A, Zamboni G. Pancreatic intraductal papillary mucinous neoplasm. In: Digestive system tumours. 5th ed. Lyon: IARC. p. 310–4.
14. Chang YR, Park JK, Jang J-Y, Kwon W, Yoon JH, Kim S-W. Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21,745 individuals. Medicine (Baltimore). 2016;95:e5535. https://doi.org/10.1097/MD.0000000000005535.
15. Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology. 2002;123:1500–7.
16. Shimada K, Sakamoto Y, Sano T, Kosuge T, Hiraoka N. Invasive carcinoma originating in an intraductal papillary mucinous neoplasm of the pancreas: a clinicopathologic comparison with a common type of invasive ductal carcinoma. Pancreas. 2006;32:281–7.
17. Mino-Kenudson M, Castillo CF, Baba Y, et al. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. Gut. 2011;60:1712–20.
18. Nara S, Shimada K, Kosuge T, Kanai Y, Hiraoka N. Minimally invasive intraductal papillary-mucinous carcinoma of the pancreas: clinicopathologic study of 104 intraductal papillary-mucinous neoplasms. Am J Surg Pathol. 2008;32:243–55.
19. Baiocchi GL, Portolani N, Missale G, Baronchelli C, Gheza F, Cantù M, Grazioli L, Giulini SM. Intraductal papillary mucinous neoplasm of the pancreas (IPMN): clinico-pathological correlations and surgical indications. World J Surg Oncol. 2010;8:25.
20. Waters JA, Schmidt CM, Pinchot JW, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg. 2008;12:101–9.
21. Furukawa T, Klöppel G, Volkan Adsay N, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Arch Int J Pathol. 2005;447:794–9.
22. Yamaguchi H, Kuboki Y, Hatori T, Yamamoto M, Shimizu K, Shiratori K, Shibata N, Shimizu M, Furukawa T. The discrete nature and distinguishing molecular features of pancreatic intraductal tubulopapillary neoplasms and intraductal papillary mucinous neoplasms of the gastric type, pyloric gland variant. J Pathol. 2013;231:335–41.
23. Adsay NV, Merati K, Andea A, Sarkar F, Hruban RH, Wilentz RE, Goggins M, Iocobuzio-Donahue C, Longnecker DS, Klimstra DS. The dichotomy in the preinvasive neoplasia to invasive carcinoma sequence in the pancreas: differential expression of MUC1 and MUC2 supports the existence of two separate pathways of carcinogenesis. Mod Pathol. 2002;15:1087–95.
24. Amato E, dal Molin M, Mafficini A, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol. 2014;233:217–27.
25. Kuboki Y, Shimizu K, Hatori T, Yamamoto M, Shibata N, Shiratori K, Furukawa T. Molecular biomarkers for progression of intraductal papillary mucinous neoplasm of the pancreas. Pancreas. 2015;44:227–35.
26. Fischer CG, Beleva Guthrie V, Braxton AM, et al. Intraductal papillary mucinous neoplasms arise from multiple independent clones, each with distinct mutations. Gastroenterology. 2019;157:1123–37.e22.
27. Kuboki Y, Fischer CG, Guthrie VB, et al. Single-cell sequencing defines genetic heterogeneity in pancreatic cancer precursor lesions. J Pathol. 2019;247:347–56.
28. Majumder S, Taylor WR, Yab TC, et al. Novel methylated DNA markers discriminate advanced neoplasia in pancreatic cysts: marker discovery, tissue validation, and cyst fluid testing. Am J Gastroenterol. 2019;114:1539–49.
29. Basturk O, Chung SM, Hruban RH, et al. Distinct pathways of pathogenesis of intraductal oncocytic papillary neoplasms and intraductal papillary mucinous neoplasms of the pancreas. Virchows Arch Int J Pathol. 2016;469:523–32.
30. Basturk O, Tan M, Bhanot U, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. Mod Pathol. 2016;29:1058–69.

31. Singhi AD, Wood LD, Parks E, et al. Recurrent rearrangements in PRKACA and PRKACB in intraductal oncocytic papillary neoplasms of the pancreas and bile duct. Gastroenterology. 2020;158:573–82.e2.
32. Simon EP, Freije CA, Farber BA, et al. Transcriptomic characterization of fibrolamellar hepatocellular carcinoma. Proc Natl Acad Sci U S A. 2015;112:E5916–25.
33. Yamaguchi H, Shimizu M, Ban S, et al. Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol. 2009;33:1164–72.
34. Basturk O, Adsay V, Askan G, et al. Intraductal tubulopapillary neoplasm of the pancreas: a clinicopathoological and immunohistochemicaol analysis of 33 cases. Am J Surg Pathol. 2017;41:313–25.
35. Basturk O, Berger MF, Yamaguchi H, et al. Pancreatic intraductal tubulopapillary neoplasm is genetically distinct from intraductal papillary mucinous neoplasm and ductal adenocarcinoma. Mod Pathol. 2017;30:1760–72.
36. Wu J, Jiao Y, Dal Molin M, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc Natl Acad Sci U S A. 2011;108:21188–93.

Chapter 16
Cancer Cell Metabolism in Pancreatic Ductal Adenocarcinoma

Hanne R. Hagland

Take Home Messages

- PDAC cells are able to grow under hypoxia by metabolic crosstalk with surrounding cells.
- KRAS mutation drives an aerobic glycolysis response in PDAC and induce nutrient scavenging by macropinocytosis.
- The ability to scavenge nutrients causes immunosuppression.
- Targeting metabolic pathways in PDAC could aid in treatment by making tumors more susceptible to chemotherapy.

Pearls and Pitfalls

- The desmoplastic nature of PDAC force cancer cells to adapt under high interstitial pressure and blood vessel collapse, resulting in nutrient scavenging and metabolic crosstalk between cancer cells and cancer associated cells.
- High interstitial pressure prevents efficient drug delivery.
- Modelling PDAC growth using co-culture organoids taken from primary tumors can better recapitulate the complexity of these tumors providing an improved test model for drug response predictions based on each tumor's metabolic profile.
- Using primary cell organoid co-cultures for treatment decisions is still in its infancy, will be more costly, laborious and require a standard operating procedure to be agreed upon before reaching its full potential in guiding clinical treatment of PDAC.

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Future Perspectives

- The increasing understanding of the complexity of PDAC tumors, with regards to metabolic crosstalk and survival mechanism, highlights potential new drug targets to be used in combination with standard treatment.
- Improved modelling systems with primary cancer cell organoids grown in co-cultures with patients own immune cells is gathering support and with improved standardized techniques may provide realistic personalized PDAC panels to perform drug screening in the future. Agreeing on standardised operational procedure in creating clinically relevant organoid systems will be imperative.
- Efforts by which tumor metabolic profiling is linked to drug susceptibility will drive the search for improving non-invasive imaging modalities and expand metabolic tracer panels, resulting in an informed picture of tumor growth *in vivo* to be used for treatment selection.
- Data from *in vivo* metabolic imaging and corresponding drug response can be used for machine learning, creating decision support systems guiding the treatment for each individual patient based on real time dynamic imaging data.

16.1 Introduction

Despite an increased understanding of the genetics and cell biology of pancreatic cancer, little has led to improved treatment effects and survival for patients with pancreatic cancer is still dismal [1]. The reason for this is multifaceted. Whereas the genetic perturbations of PDAC is dominated by three or four commonly altered somatic mutations in *KRAS*, *TP53*, *SMAD4* and *CDKN2A* [2], these targets are not easily druggable as they control many growth regulatory processes in normal as well as cancer cells [3]. Further, a well-described feature of PDAC is the desmoplastic growth pattern [4], resulting in vascular collapse and tumor hypoperfusion, limiting not only oxygen and nutrient availability to the cancer cells [5] but also hindering drug delivery [6] and cell waste disposal.

Cancer cells need a continuous source of nutrients to create biomass for building new cells and cannot grow under nutrient deprivation, nor under complete anoxia (i.e. 0% oxygen). Low levels of oxygen (hypoxia) and scarce nutrient availability are commonly found in PDAC [5]. Hypoxia leads to an increase in reactive oxygen species (ROS) within the cell, and nutrient scarity causes a reduction in supply of non-essential amino acids versus essential amino acids. Both may cause a more acidic tumor microenvironment when blood vessel vasculature collapses (Fig. 16.1) [7]. Hence, the metabolic rewiring in PDAC has evolved to sustain growth under harsh conditions with limited substrate supply, and lack of ordered cell waste disposal, both normally handeled by the normal vasculature.

The focus in this chapter is the metabolic adaptation and metabolic crosstalk between cancer cells and their microenvironment, which can be tissue specific due to growth circumstances and has been termed metabolic addiction [8]. A better understanding of this metabolic crosstalk and complexity holds promise to find new potential treatment targets for patients with PDAC.

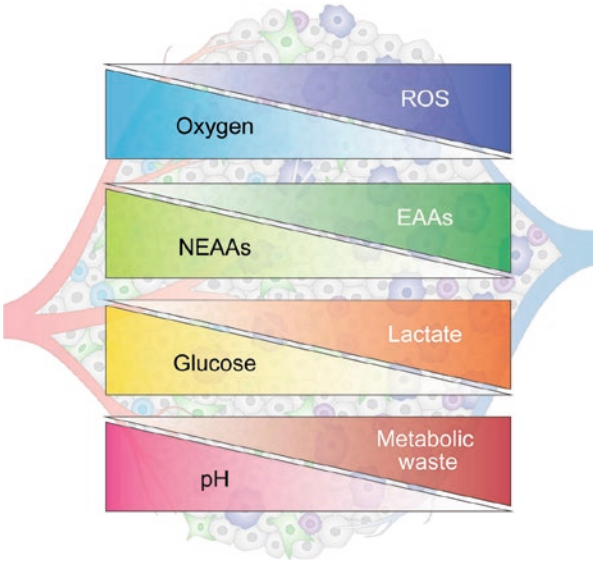

Fig. 16.1 Metabolic gradients in tumors. The metabolic activity of cancer cells and stromal cells as well as proximity to the vasculature contribute to the formation of metabolic gradients within tumors. In hypovascularized tumor core regions (right), glucose, glutamine, and other non essential amino acids (NEAAs) are depleted, while certain essential amino acids (EAAs) and metabolic waste products such as lactate accumulate. These areas are also characterized by elevated levels of ROS and acidic pH. (Reprinted from Ref. [7], (https://doi.org/10.1016/j.cmet.2019.01.015) with copyright permission from Elsevier (2019))

16.2 Normal and Cancer Cell Metabolism: *The Warburg Effect*

16.2.1 Energy Substrates and Glucose Homeostasis

The main energy substrates used in metabolism are carbohydrates, lipids and proteins. How the body utilizes these substrates depends on the metabolic state (fed or starved), type of tissue, energetic demand (exercise or resting) and oxygen availability. After digestion the available nutrients are monosaccharides (glucose, dextrose, galactose), fatty acids and non-essential and essential amino acids for the cells to import according to their needs.

Non-dividing cells in the parenchymal tissues (in pancreas such as exocrine acini ducts and the endocrine islets of Langerhans) typically metabolize glucose intracellularly via glycolysis to pyruvate, which can then enter the mitochondria fueling the tricarboxylic acid (TCA) cycle.

The first step in the TCA cycle is oxidation of acetyl-CoA, which can be derived from carbohydrates (glucose breakdown), fats (fatty acid β-oxidation) or proteins (certain amino acids feed into the cycle as acetyl-CoA, others such as glutamine or glutamate enter as alpha-ketoglutarate) where each TCA cycle produces electrons

donated to the electron transport chain in the inner mitochondrial membrane. In the mitochondria the electron transport chain uses the energy from the electrons to create a membrane potential between the matrix and intermembrane space, necessary for making adenosine triphosphate (ATP) by oxidative phosphorylation (Fig. 16.2) [9]. One glucose molecule results in about 36 ATP molecules when fully metabolized through these pathways in the presence of oxygen, whereas in hypoxia this glucose breakdown is significantly less efficient, providing a net production of only 2 ATP per glucose molecule through glycolysis with lactate as waste product.

Interestingly, cancer cells revert to mainly using the glycolytic pathway and not mitochondria for glucose break down, even when there is normal supply of oxygen, thus producing high levels of lactate to the surrounding tumor microenvironment. This metabolic switch was described nearly a century ago by the German physician Otto Warburg [10], and is called "*the Warburg effect*" (Box 16.1).

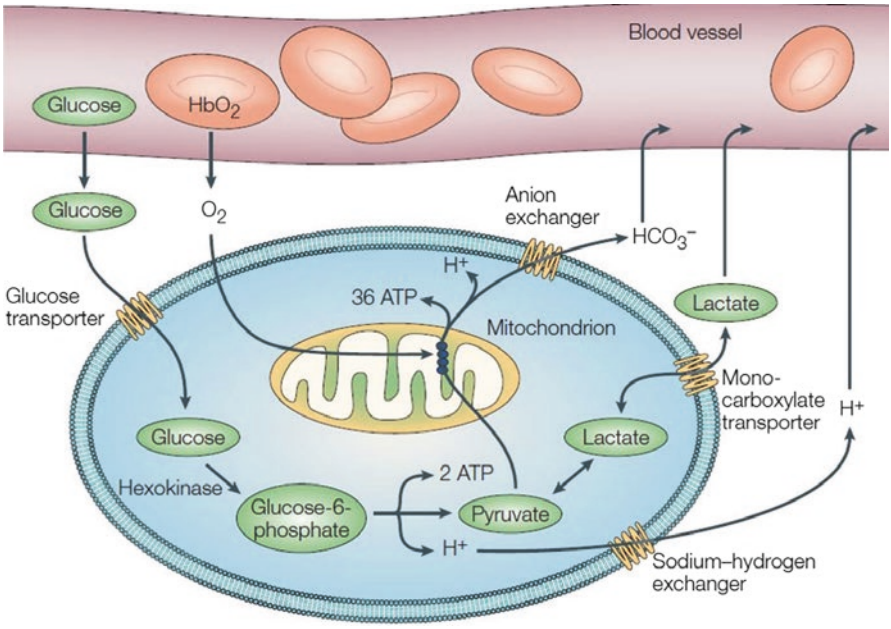

Fig. 16.2 Glucose metabolism in mammalian cells. Afferent blood delivers glucose and oxygen (on haemoglobin) to tissues, where it reaches cells by diffusion. Glucose is taken up by specific transporters, where it is converted first to glucose-6-phosphate by hexokinase and then through several subsequent steps to pyruvate, generating 2 ATP per glucose molecule. In the presence of oxygen, pyruvate is oxidized to HCO_3, generating 36 additional ATP per glucose. In the absence of oxygen, pyruvate is reduced to lactate, which is exported from the cell. Note that both processes produce hydrogen ions (H^+), which cause acidification of the extracellular space. *HbO_2* oxygenated haemoglobin. (Reprinted from Ref. [12], with copyright permission from Springer Nature (2004))

Box 16.1 Otto Heinrich Warburg (1883–1970), German Physician and Scientist

The Nobel Prize in Physiology or Medicine 1931 was awarded to Otto Heinrich Warburg "***for his discovery of the nature and mode of action of the respiratory enzyme***." In our cells nutrients are broken down so that energy is released for the construction of cells. This respiration requires enzymes, substances that facilitate the process without being incorporated in the final products. Otto Warburg studied the respiration of sea urchins and other organisms at an early stage of development. By measuring oxygen consumption in living cells and studying which enzymes reacted, in 1928 he concluded that the respiration enzyme he was looking for was a red ferrous pigment related to the blood pigment, hemoglobin. "Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by fermentation of sugar."

Photo from the Nobel Foundation archive, from https://www.nobelprize.org/prizes/medicine/1931/summary/

Experiments linking the metabolic switch in cancer cells to frequently mutated oncogenes and tumor suppressor genes, by studying cancer cell models, have increased our understanding how this translates in altered cell metabolism [9, 11, 12]. The metabolic switch is one of the hallmarks of cancer [13] and is a result from increased demand for cell biomass (proteins and lipids) and nucleotides for DNA replication when producing a new daughter cell during cell proliferation.

Glucose, fatty acids and amino acids from the blood vasculature or extracellular environment, all contribute to the biomass needed to build a new cell. These biosynthetic requirements are universal for all replicating cells, not just cancer cells, thus under strict control by growth factor signalling, pathways often found dysregulated in cancer [9, 14]. A prime example of normal cells with a superior ability to exploit this metabolic switch are the cells of the adaptive immune system (i.e. T-lymphocytes), which revert to this form of metabolism upon antigen presentation leading to their rapid clonal expansion (cell proliferation) [15]. The interplay between PDAC and

immune cells (see Chap. 21 in this textbook) will only be discussed in relation to nutrient availability in the tumor microenvironment and how this can influence the type of immune response seen near the tumor.

Warburg's hypothesis was that the increase in glucose flux in cancer was due to deficient mitochondria [10], however although mutations in mitochondrial genes are common in cancer cells, the mitochondria are important contributers for providing the proliferating cells with intermediates used for biomass [16]. Tumor cells in oxygen rich environments (i.e. near blood vessels) utilize both aerobic glycolysis and oxidative phosphorylation to sustain their rapid rates of proliferation [17], and the mitochondria are important in supporting their proliferation. However, these mitochondria are using other fuels or intermediates than pyruvate from glycolysis to support the flux of their TCA cycle [18, 19]. In PDAC, cancer cells exploit these metabolic pathways for their growth and survival benefits. The metabolic behavior alters the composition of the extracellular environment and influence both the growth of supporting cells and the immune response.

16.2.2 PDAC Progression: Driver Mechanisms

PDAC has an established progression model for development, where the normal duct epithelium progresses to invasive adenocarcinoma through histologically well-defined stages of duct lesions, the so-called pancreatic intraepithelial neoplasias (PanINs) [20, 21]. Somatic alterations with activating mutations in *KRAS* (*>90%*), inactivating mutations in *CDKN2A*, *TP53* and *SMAD4* (range of 50–80% prevalence) are the major driver mutations found in PDAC and all are shown to arise in PanINs [21, 22]. Advances in sequencing technology have allowed for a greater number of PDAC to be sequenced since this progression model was proposed. However, the main genetic lesions have been consistent, suggesting that a saturation point in the discovery phase of high-frequency genetic targets in pancreatic cancer has been reached [23].

Although oncogenic *KRAS* mutations are found in nearly all PDAC cancers [24], it is also found in the normal pancreatic cells of patients with no evidence of cancer, suggesting that this mutation is an early event in the oncogenic process and whilst important, not sufficient to result in PDAC. Mutations in *KRAS* leading to increased or constitutively active expression, can induce a series of metabolic alterations, which includes enhanced ability to scavenge nutrients and increased glycolysis and glutaminolysis (glutamine metabolism) [25, 26].

KRAS is a key regulator downstream of growth factor receptor activation and act as an 'on switch' for all intracellular processes that is in support of anabolic metabolism (energy demanding processes, i.e. cell replication). Further loss of growth control through mutations in tumor suppressor genes such as *CDKN2*, *TP53* and *SMAD4* will create a growth advantage for these cells and may ultimately lead to a full blown cancer. These genes may represent the necessary underlying genetic perturbations for turning on the metabolic machinery needed to support cell growth in these cancers. Other factors that are causing further cancer progression will be presented in the next sub chapters.

16.3 Tumor Microenvironment in PDAC

16.3.1 Physical Changes Driving the Metabolic Switch

The PDAC cancers are unique in that nearly 90% of the tumor volume consist of extensive desmoplastic stroma [27], composed of extracellular matrix proteins such as collagens, fibronectins and laminins, as well as non-collagenous proteins such as glycoproteins, proteoglycans and glycosaminoglycans. Cells found in the microenvironment include pancreatic stellate cells, infiltrating immune cells, endothelial cells and neuronal cells. The pancreatic stellate cells in particular can transform to cancer associated fibroblasts by nearby cancers cells, supporting the growth of the cancer cells and substantially increase the production of extracellular matrix components [28].

The extracellular matrix produced by the cancer associated fibroblasts is rich in hyaluronic acid, a negatively charged glycosaminoglycan, that binds large amounts of water leading to high interstitial fluid pressure [29]. The increased interstitial fluid pressure can exceed ten times that observed in a normal pancreas [30], resulting in widespread vascular collapse and hypoperfusion [23], which is commonly observed in PDAC cancers. Furthermore, this dense fibrotic stroma and increased interstitial fluid pressure may create isolated regions of neoplastic cells, apart from their initial tumor site. These scattered regions of neoplastic cells can then adapt to their unique growth conditions, increasing the intratumoral heterogeneity often found in PDAC [23]. Another result of high interstitual pressure is a dysfunctional vascular system leading to oxygen deprivation, creating states of hypoxia commonly seen in cancer (below 2% oxygen) [31, 32]. Cells in hypoxic regions can survive by triggering a metabolic stress response activated by the hypoxic sensor and transcriptional regulator; hypoxia inducible factor 1 alpha (HIF1α), being a master regulator of genes involved in glucose metabolism. These include upregulation of the glucose transporter protein 1 (GLUT1), as well as the protein responsible for the first step in glycolysis Hexokinase-2 (HK-2) [33]. Like HIF1α, activation of MYC and TP53 deactivation cause an increase in GLUT1 and HK-2 expression supporting the growth of PDAC cancers [34]. Both MYC and TP53 are commonly found mutated in PDAC [17]. MYC activation increases the uptake of important amino acids, such as glutamine, from the tumor microenvironment, where these amino acids act as important anaplerotic substrates to fuel the TCA cycle in the mitochondria. The intermediates coming from the TCA cycle is particularly important in conditions where carbon from glucose is broken down through glycolysis to lactate, supplying the glycolytic derived intermediary pathways [35], but not supplying the mitochondrion with enough pyruvate substrate.

In PDAC the glutamine demand is high, and cannot be supported by uptake from the extracellular environment alone, resulting in an upregulation of intracellular glutamine synthesis supported by increased expression of glutamine ammonia ligase (GLUL) [35]. GLUL-mediated glutamine biosynthesis is coupled to TCA cycle promoting nitrogen-dependent processes such as the making of new nucleotides and hexosamines needed for DNA replication. This recently discovered feature of PDAC, makes these tumors self-sufficient in glutamine supply, even where

the circulatory system is limited and could provide a new interesting target for PDAC treatment.

16.3.2 Immune Suppression

Pancreatic cancers are thought to be slow growing and develop during the course of nearly two decades until giving clinical signs of disease [36]. During the course of oncogenesis the cancer cells shape their microenvironment to support the continued proliferation at the expense of the other cell types found in its surrounding. In particular immune cells from both the innate and adaptive immune system are affected by the cancer growth as they heavily depend on nutrient availability in their growth environment (Fig. 16.3).

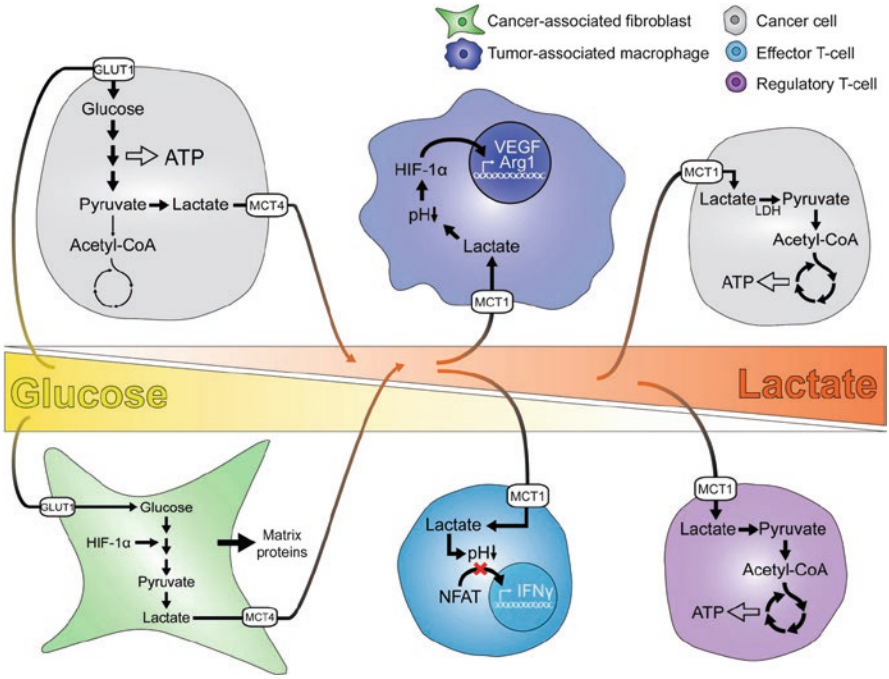

Fig. 16.3 Lactate's effects on tumor and stromal cells. Glucose is present in high levels in proximity to the vasculature (left) and is consumed by tumor cells and cancer-associated fibroblasts. Glucose consumption is coupled to lactate secretion, resulting in lactate accumulation with increasing distance from the efferent vasculature. In poorly vascularized regions (right), cancer cells and regulatory T cells are able to metabolize lactate to sustain energy homeostasis. In contrast, lactate exerts paracrine effects on tumor-associated macrophages and effector T cells, stimulating differentiation of macrophages into an immunosuppressive M2-like phenotype and suppressing T cell effector function. (Reprinted from Ref. [7], (https://doi.org/10.1016/j.cmet.2019.01.015) with copyright permission from Elsevier (2019))

The induction of T-cells to cytotoxic $CD8^+$ T-cells, part of the adaptive immune response that mount immune attacks upon the presentation of a foreign antigen, require a metabolic switch for the cells to be able to proliferate to high numbers upon activation. This activatoin process is reliant on glucose, where depletion of glucose in the tumor microenvironment has an immunosuppressive function [37]. The same is true for the innate immune response where attacking M1 macrophages, producing inflammatory cytokines, are inhibited due to low substrate and oxygen tension, thereby transforming them to tolerogenic M2 macrophages commonly found in PDAC [38]. This substrate induced immunosuppression in the tumor microenvironment is an area of intense study and has shown that nutrients can regulate whether T-cells adapt to a less aggressive regulatory phenotype ($CD4^+$) rather than a cancer attacking cytotoxic T-cell ($CD8^+$) [39]. Recent studies show that the metabolic switch to glycolysis in cancer cells inhibit the expression of the major histocompatibility complex receptor 1 (MHC1), needed for activation of cytotoxic T-cells, which supports that targeting cancer cell metabolism could potentially improve immunotherapeutic success [40].

16.3.3 Metabolic Crosstalk

Mechanism by which cancer cells might direct the fate of stromal cells within the tumor is by altering the metabolic composition of the extracellular environment through the consumption of available nutrients and secretion of metabolic 'waste' products. Glucose is rapidly depleted from the tumor microenvironment [5], while cell lactate that is exported out via the monocarboxylate transporter system in cotransport with H^+ ions, causes acidification of the local environment [41]. Nutrients (i.e. glucose) and cell waste (i.e. lactate) are charged molecules unable to diffuse through the phospholipid bilayer of the cell membrane, where both the affinity of the receptors to their substrate as well as the number of receptors regulate the import and export of these in and out of the cell. The glucose import is regulated by GLUTs, whereas the excess lactate produced under aerobic glycolysis is transported out of the cell through different isoforms of monocarboxylate transporters [42]. Monocarboxylate transporter 1 (MCT1) is ubiquitously expressed in most tissues, whereas MCT4 (lower affinity to lactate, i.e. higher concentrations of lactate to activate it) expression is confined to highly glycolytic cell types such as fast-twitch muscle fibers [43] or in cells induced under hypoxia by HIF1α [44].

MCT1 and MCT4 have been shown to act in metabolic crosstalk between PDAC cells in normoxic versus hypoxic areas, where MCT1 is more widely expressed under normoxia and MCT4 in hypoxia [8] (Fig. 16.4). Thus, tumor cells can variably excrete and utilize lactate in a manner that may depend on the extracellular environment. Metabolic tracing studies suggest that both glucose and lactate are significant nutrient sources for cancers *in vivo* [45, 46], where oxygen levels influence the nutrient of choice.

Another common ability of PDAC cancers is using macropinocytosis to scavenge proteins from the extracellular environment to support the growth during nutrient

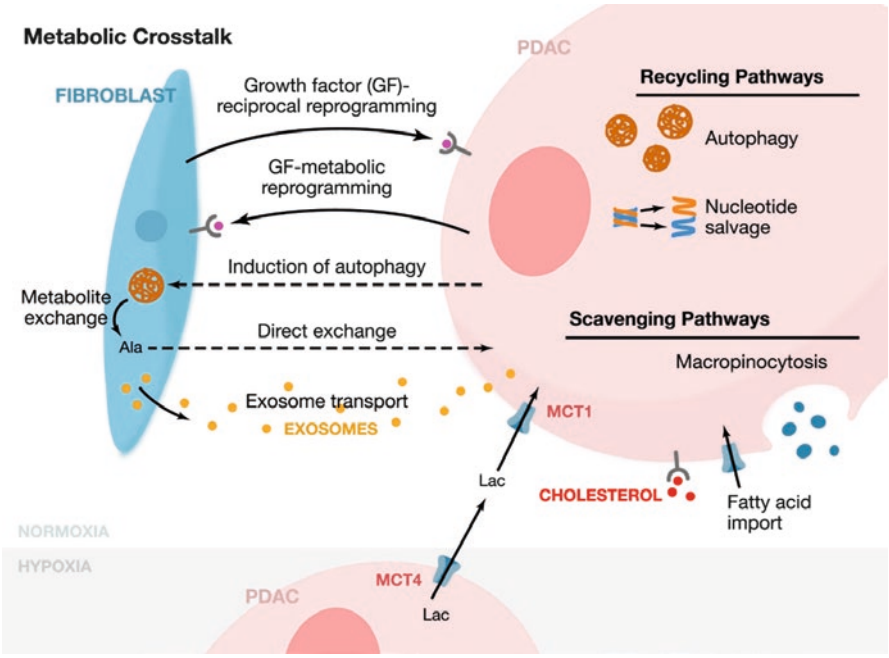

Fig. 16.4 Methods of nutrient acquisition utilized by PDAC. Pancreatic cancer cells engage in metabolic crosstalk with stromal cells by multiple avenues. Growth factors (GF) released from the PDAC cells can metabolically reprogram fibroblasts, which respond by the release of different GFs capable of reciprocal reprogramming of the epithelial cells. PDAC cells also induce autophagy in pancreatic stellate cells, stimulating the release of growth-promoting alanine (Ala). Metabolite exchange also occurs among cancer cells, as PDAC cells in hypoxic environments release lactate (Lac) which fuels proliferation in normoxic cancer cells. Pancreatic cancer cells are capable of utilizing recycling pathways and engage in multiple mechanisms of scavenging extracellular nutrient sources, including non-specific macropinocytosis and lipid uptake, to obtain nutrients in the austere pancreatic tumor microenvironment. (Reprinted from Ref. [8] (https://doi.org/10.1016/j.ccell.2016.12.006), with copyright permissions from Elsevier (2016))

deprived conditions [5]. Macropinocytosis is the active uptake of extracellular fluids by actin mediated cell membrane extensions that folds inwards, resulting in endocytic vesicles with degraded proteins to be used as nutrients (Fig. 16.4). PDAC can induce an autophagic response in cancer associated fibroblasts, that supply the cancer cells with non-essential amino acids to be taken up via macropinocytosis from the tumor microenvironment fueling the TCA cycle [47] in nutrient scarce conditions. PDAC with oncogenic KRAS has increased ability for using macropinocytosis, giving them a growth advantage at both nutrient replete conditions as well as an ability to survive under nutrient deprived conditions [48].

The complexity of bidirectional metabolic crosstalk between tumour and its microenvironment can only be modelled *in vitro* to a certain point, which underscores the importance of finding relevant *in vivo* models to further study these interactions. There are technical challenges of interrogating metabolic fluxes *in vivo*, and

although the use of ^{18}fluoro-2-deoxyglucose positron emission tomography (FDG-PET) gives a visual read of the glucose consumption of the tumors, it does not reflect the complexity of glucose metabolism derivatives downstream, which is affected by both cell intrinsic and extrinsic signalling [46]. However, two previous studies in selected patient cohorts have addressed this challenge by administring stable glucose isotope (e.g. ^{13}C) infusions to the patients before tumor resections, and performing subsequent analysis of metabolites enriched with ^{13}C [46, 49] in the excised tissue. More such studies may provide new insight to better understand the complexity of tumor metabolism *in vivo*. However, this requires a well-coordinated interdisciplinary collaboration regarding each patient, which is both labour intensive and time sensitive [46]. Table 16.1 gives an overview of old and new cancer models used to better understand the complexity of PDAC with their advantages and challenges.

Table 16.1 Overview of different model systems for studying pancreatic cancer

Model system	Cells	Advantages	Challenges	References
Organoids	Primary tumor cells and supportive fibroblasts	Recapitulate the patients tumor growing in 3D	Requires sufficient amount of tissue to get cell cultures growing; small tumor biopsies are difficult to grow	[50–53]
Spheroids	Established cell lines grown in 3D often with collagen I simulating extracellular matrix	Easy to culture, could give useful information in regards to drug responses if linked to genetic and metabolic profiling	Difficult to recapitulate the heterogeneity of each patient tumor, thus limiting the clinical application for guiding in personalised drug treatment	[54–56]
Xenografts	Tumor cells engrafted into mice, either at tumor origin site (if possible) or subcutaneously	Drug delivery resembles that of human with a natural metabolism of the drug over time which is difficult to mimic in static *in vitro* experiments	Subcutaneous xenografts show little resemblance to tumor derived growth conditions lacking the complexity of immune and fibroblast cells. Immunocompromised mice used for xenograft models do not mimic the settings found in humans	[54, 57, 58]
Organoid co-culture	Primary tumor cells co-cultured with immune cells from peripheral blood and tumor associated fibroblast	Can recapitulate the uniqueness of each patients tumor and be used for drug screening to predict best treatment, patients own immune and cancer cells are used	Is time and labour intensive, results from drug screening in co-culture organoids may take up to 1 month, making it challenging for rapid decision support	[59, 60]

16.4 Treatment Challenges in PDAC with Respect to Metabolism

Most PDAC patients who undergo surgery will develop recurrent disease, showing evidence that small populations of cancer cells are left behind either in the pancreas or systemically. How these residual cancer cells manage to survive after systemic chemotherapy or radiation is unknown, but both the metabolic flexibility and mitochondrial function of these residual cells are suggested to play a role [61].

The robust nature of the PDAC cells to adapt to their growth conditions and survive under both hypoxia and nutrient deprivation is very likely to give them added abilities to overcome the attack from conventional cancer treatment. PDAC cells in hypoxic areas will be more resistant to radiotherapy since this treatment uses oxygen to create high levels of reactive oxygen species targeting the cancer [62]. However, although PDAC growth induce immunosuppression (Fig. 16.3), radiotherapy has shown to reprogram the tumor infiltrating macrophages from tolerogenic M2 to attacking M1 state and increase the presence of cytotoxic T-cells in the tumor area [58, 63, 64]. Ongoing clinical trials to test the combination of radiotherapy with immunotherapy may provide insight as to a potential future course of treatment (NCT03767582).

The unique metabolism of PDAC cells, could also become their Achilles heel, and inhibitors of mitochondrial oxidative phosphorylation (OXPHOS) are currently ongoing (NCT03699319) and set to be explored in clinical trials for patients targeting the cells surviving in normoxic areas of the tumor where mitochondrial function plays an important role [65]. Small inhibitors for lactate dehydrogenase, acting to reduce the conversion of pyruvate to lactate, has been tested in a phase I clinical trial for metastatic colorectal cancer (NCT00540722) and could be an interesting drug to test targeting the glycolytic PDAC cancer cells thriving in hypoxic conditions [8]. The high interstitial fluid pressure in PDAC cancers confers challenges of delivering drugs via the bloodstream to the tumour. A small phase I trial using microbubbles-directed delivery of gemcitabine (“sonoporation”, see separate chapter) by ultrasound treatment showed promising results [66]. Increased understanding of the metabolic effects to tumor growth and patient prognosis, will make it possible to overcome many stroma-mediated therapeutic barriers in the future [7].

16.5 Conclusion

Understanding how the cellular and metabolic composition of the tumor microenvironment determines the growth phenotype is crucial to improve current PDAC treatment and exploit these novel vulnerabilities. In particular, successful therapeutic strategies have to take into account the complex relationships between different cell populations within the tumour microenvironment that are subject to dynamic changes in nutrient supply, particularly in response to therapy.

Future clinical trials should consider metabolic compensation and at start recording nutritional parameters of their participants for expanding our knowledge in this field. It is evident that clinical performance of single agent treatment therapies as is the standard, has been in large effect unsuccessful for these patients and new intelligent combinations are called for. Only by application of the full repertoire of clinical toolkits, such as genetic, epigenetic and metabolic changes in tumors over time will improve proper patient stratification and specific temporal monitoring of treatment response [67].

For more targeted treatments, the use of patients own cancer cells for making organoids to be screened *in vitro* [51] for a panel of drugs is an area currently expanding and shows promising results. Another area which may improve clinical decisions in the future is the use of metabolic tracers *in vivo*. However real time acquisition of metabolic tracers currently has limited spatial resolution when used in the patients, and should be an area of research to be addressed in the years to come.

Finally, the PDAC patients do not only suffer from lack of treatment options, the mode of drug delivery is also a challenge and an area under investigation. Hopefully, more realistic modelling systems giving an increased understanding of how metabolic crosstalk play a role in developing the desmoplastic nature of PDAC and inhibit drug response, can be coupled to clinical trials with metabolic and nutritional patient recordings that can advance the treatment of PDAC in the future.

References

1. Rahib L, Fleshman JM, Matrisian LM, Berlin JD. Evaluation of pancreatic cancer clinical trials and benchmarks for clinically meaningful future trials: a systematic review. JAMA Oncol. 2016;2:1209–16. https://doi.org/10.1001/jamaoncol.2016.0585.
2. Waddell N, Pajic M, Patch A-M, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518:495–501. https://doi.org/10.1038/nature14169.
3. Aguirre AJ, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. Cancer Discov. 2018;8:1096–111. https://doi.org/10.1158/2159-8290.CD-18-0275.
4. Sousa CM, Kimmelman AC. The complex landscape of pancreatic cancer metabolism. Carcinogenesis. 2014;35:1441–50. https://doi.org/10.1093/carcin/bgu097.
5. Kamphorst JJ, Nofal M, Commisso C, Hackett SR, Lu W, Grabocka E, et al. Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. Cancer Res. 2015;75:544–53. https://doi.org/10.1158/0008-5472.CAN-14-2211.
6. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009;324:1457–61. https://doi.org/10.1126/science.1171362.
7. Schwörer S, Vardhana SA, Thompson CB. Cancer metabolism drives a stromal regenerative response. Cell Metab. 2019;29:576–91. https://doi.org/10.1016/j.cmet.2019.01.015.
8. Halbrook CJ, Lyssiotis CA. Employing metabolism to improve the diagnosis and treatment of pancreatic cancer. Cancer Cell. 2017;31:5–19. https://doi.org/10.1016/j.ccell.2016.12.006.
9. Lunt SY, Van der Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annu Rev Cell Dev Biol. 2011;27:441–64. https://doi.org/10.1146/annurev-cellbio-092910-154237.

10. Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol. 1927;8:519–30.
11. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. Cell Metab. 2016;23:27–47. https://doi.org/10.1016/j.cmet.2015.12.006.
12. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer. 2004;4:891–9. https://doi.org/10.1038/nrc1478.
13. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74. https://doi.org/10.1016/j.cell.2011.02.013.
14. Zhu J, Thompson CB. Metabolic regulation of cell growth and proliferation. Nat Rev Mol Cell Biol. 2019;20:436–50. https://doi.org/10.1038/s41580-019-0123-5.
15. Dimeloe S, Burgener A-V, Grählert J, Hess C. T-cell metabolism governing activation, proliferation and differentiation; a modular view. Immunology. 2017;150:35–44. https://doi.org/10.1111/imm.12655.
16. Wallace DC. Mitochondria and cancer. Nat Rev Cancer. 2012;12:685–98. https://doi.org/10.1038/nrc3365.
17. Le A. The Heterogeneity Of Cancer Metabolism. Cham: Springer International Publishing; 2018.
18. Porporato PE, Filigheddu N, Pedro JMB-S, Kroemer G, Galluzzi L. Mitochondrial metabolism and cancer. Cell Res. 2018;28:265–80. https://doi.org/10.1038/cr.2017.155.
19. Zu XL, Guppy M. Cancer metabolism: facts, fantasy, and fiction. Biochem Biophys Res Commun. 2004;313:459–65. https://doi.org/10.1016/j.bbrc.2003.11.136.
20. Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol. 2001;25:579–86. https://doi.org/10.1097/00000478-200,105,000-00003.
21. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res. 2000;6:2969–72.
22. Murphy SJ, Hart SN, Lima JF, Kipp BR, Klebig M, Winters JL, et al. Genetic alterations associated with progression from pancreatic intraepithelial neoplasia to invasive pancreatic tumor. Gastroenterology. 2013;145:1098–1109.e1. https://doi.org/10.1053/j.gastro.2013.07.049.
23. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer. 2016;16:553–65. https://doi.org/10.1038/nrc.2016.66.
24. Waters AM, Der CJ. KRAS: the critical driver and therapeutic target for pancreatic cancer. Cold Spring Harb Perspect Med. 2018; https://doi.org/10.1101/cshperspect.a031435.
25. Kumari S, Khan S, Gupta SC, Kashyap VK, Yallapu MM, Chauhan SC, Jaggi M. MUC13 contributes to rewiring of glucose metabolism in pancreatic cancer. Oncogenesis. 2018;7:19. https://doi.org/10.1038/s41389-018-0031-0.
26. Ying H, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sananikone E, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell. 2012;149:656–70. https://doi.org/10.1016/j.cell.2012.01.058.
27. Dougan SK. The pancreatic cancer microenvironment. Cancer J. 2017;23:321–5. https://doi.org/10.1097/PPO.0000000000000288.
28. Masamune A, Shimosegawa T. Pancreatic stellate cells: a dynamic player of the intercellular communication in pancreatic cancer. Clin Res Hepatol Gastroenterol. 2015;39(Suppl 1):S98–103. https://doi.org/10.1016/j.clinre.2015.05.018.
29. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut. 2013;62:112–20. https://doi.org/10.1136/gutjnl-2012-302,529.
30. Provenzano PP, Cuevas C, Chang AE, Goel VK, von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21:418–29. https://doi.org/10.1016/j.ccr.2012.01.007.
31. McKeown SR. Defining normoxia, physoxia and hypoxia in tumours-implications for treatment response. Br J Radiol. 2014;87:20130676. https://doi.org/10.1259/bjr.20130676.

32. Lawrentschuk N, Poon AMT, Foo SS, Putra LGJ, Murone C, Davis ID, et al. Assessing regional hypoxia in human renal tumours using 18F-fluoromisonidazole positron emission tomography. BJU Int. 2005;96:540–6. https://doi.org/10.1111/j.1464-410X.2005.05681.x.
33. Yang W, Lu Z. Regulation and function of pyruvate kinase M2 in cancer. Cancer Lett. 2013;339:153–8. https://doi.org/10.1016/j.canlet.2013.06.008.
34. Hessmann E, Schneider G, Ellenrieder V, Siveke JT. MYC in pancreatic cancer: novel mechanistic insights and their translation into therapeutic strategies. Oncogene. 2016;35:1609–18. https://doi.org/10.1038/onc.2015.216.
35. Bott AJ, Shen J, Tonelli C, Zhan L, Sivaram N, Jiang Y-P, et al. Glutamine anabolism plays a critical role in pancreatic cancer by coupling carbon and nitrogen metabolism. Cell Rep. 2019;29:1287–1298.e6. https://doi.org/10.1016/j.celrep.2019.09.056.
36. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature. 2010;467:1114–7. https://doi.org/10.1038/nature09515.
37. Zhang Y, Kurupati R, Liu L, Zhou XY, Zhang G, Hudaihed A, et al. Enhancing CD8+ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. Cancer Cell. 2017;32:377–391.e9. https://doi.org/10.1016/j.ccell.2017.08.004.
38. Carmona-Fontaine C, Deforet M, Akkari L, Thompson CB, Joyce JA, Xavier JB. Metabolic origins of spatial organization in the tumor microenvironment. Proc Natl Acad Sci U S A. 2017;114:2934–9. https://doi.org/10.1073/pnas.1700600114.
39. Angelin A, Gil-de-Gómez L, Dahiya S, Jiao J, Guo L, Levine MH, et al. Foxp3 reprograms T cell metabolism to function in low glucose high lactate environments. Cell Metab. 2017;25:1282–1293.e7. https://doi.org/10.1016/j.cmet.2016.12.018.
40. Marijt KA, Sluijter M, Blijleven L, Tolmeijer SH, Scheeren FA, van der Burg SH, van Hall T. Metabolic stress in cancer cells induces immune escape through a PI3K-dependent blockade of IFNγ receptor signaling. J Immunother Cancer. 2019;7:152. https://doi.org/10.1186/s40425-019-0627-8.
41. Schornack PA, Gillies RJ. Contributions of cell metabolism and H+ diffusion to the acidic pH of tumors. Neoplasia. 2003;5:135–45. https://doi.org/10.1016/S1476-5586(03)80005-2.
42. Halestrap AP, Price NT. The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochem J. 1999;343:281–99.
43. Dimmer KS, Friedrich B, Lang F, Deitmer JW, Bröer S. The low-affinity monocarboxylate transporter MCT4 is adapted to the export of lactate in highly glycolytic cells. Biochem J. 2000;350:219–27.
44. Ullah MS, Davies AJ, Halestrap AP. The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. J Biol Chem. 2006;281:9030–7. https://doi.org/10.1074/jbc.M511397200.
45. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, et al. Lactate metabolism in human lung tumors. Cell. 2017;171:358–371.e9. https://doi.org/10.1016/j.cell.2017.09.019.
46. Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, et al. Metabolic heterogeneity in human lung tumors. Cell. 2016;164:681–94. https://doi.org/10.1016/j.cell.2015.12.034.
47. Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, et al. Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. Nature. 2016;536:479–83. https://doi.org/10.1038/nature19084.
48. Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature. 2013;497:633–7. https://doi.org/10.1038/nature12138.
49. Maher EA, Marin-Valencia I, Bachoo RM, Mashimo T, Raisanen J, Hatanpaa KJ, et al. Metabolism of U-13 Cglucose in human brain tumors in vivo. NMR Biomed. 2012;25:1234–44. https://doi.org/10.1002/nbm.2794.
50. Moreira L, Bakir B, Chatterji P, Dantes Z, Reichert M, Rustgi AK. Pancreas 3D organoids: current and future aspects as a research platform for personalized medicine in pancreatic cancer. Cell Mol Gastroenterol Hepatol. 2018;5:289–98. https://doi.org/10.1016/j.jcmgh.2017.12.004.

51. Hou S, Tiriac H, Sridharan BP, Scampavia L, Madoux F, Seldin J, et al. Advanced development of primary pancreatic organoid tumor models for high-throughput phenotypic drug screening. SLAS Discov. 2018;23:574–84. https://doi.org/10.1177/2472555218766842.
52. Tiriac H, Belleau P, Engle DD, Plenker D, Deschênes A, Somerville TDD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. Cancer Discov. 2018;8:1112–29. https://doi.org/10.1158/2159-8290.CD-18-0349.
53. Broutier L, Andersson-Rolf A, Hindley CJ, Boj SF, Clevers H, Koo B-K, Huch M. Culture and establishment of self-renewing human and mouse adult liver and pancreas 3D organoids and their genetic manipulation. Nat Protoc. 2016;11:1724–43. https://doi.org/10.1038/nprot.2016.097.
54. Izumchenko E, Paz K, Ciznadija D, Sloma I, Katz A, Vasquez-Dunddel D, et al. Patient-derived xenografts effectively capture responses to oncology therapy in a heterogeneous cohort of patients with solid tumors. Ann Oncol. 2017;28:2595–605. https://doi.org/10.1093/annonc/mdx416.
55. Beer M, Kuppalu N, Stefanini M, Becker H, Schulz I, Manoli S, et al. A novel microfluidic 3D platform for culturing pancreatic ductal adenocarcinoma cells: comparison with in vitro cultures and in vivo xenografts. Sci Rep. 2017;7:1325. https://doi.org/10.1038/s41598-017-01256-8.
56. Broekgaarden M, Anbil S, Bulin A-L, Obaid G, Mai Z, Baglo Y, et al. Modulation of redox metabolism negates cancer-associated fibroblasts-induced treatment resistance in a heterotypic 3D culture platform of pancreatic cancer. Biomaterials. 2019;222:119421. https://doi.org/10.1016/j.biomaterials.2019.119421.
57. Sereti E, Karagianellou T, Kotsoni I, Magouliotis D, Kamposioras K, Ulukaya E, et al. Patient derived xenografts (PDX) for personalized treatment of pancreatic cancer: emerging allies in the war on a devastating cancer? J Proteomics. 2018;188:107–18. https://doi.org/10.1016/j.jprot.2018.01.012.
58. Kalbasi A, Komar C, Tooker GM, Liu M, Lee JW, Gladney WL, et al. Tumor-derived CCL2 mediates resistance to radiotherapy in pancreatic ductal adenocarcinoma. Clin Cancer Res. 2017;23:137–48. https://doi.org/10.1158/1078-0432.CCR-16-0870.
59. Cattaneo CM, Dijkstra KK, Fanchi LF, Kelderman S, Kaing S, van Rooij N, et al. Tumor organoid-T-cell coculture systems. Nat Protoc. 2020;15:15–39. https://doi.org/10.1038/s41596-019-0232-9.
60. Tsai S, McOlash L, Palen K, Johnson B, Duris C, Yang Q, et al. Development of primary human pancreatic cancer organoids, matched stromal and immune cells and 3D tumor microenvironment models. BMC Cancer. 2018; https://doi.org/10.1186/s12885-018-4238-4.
61. Viale A, Corti D, Draetta GF. Tumors and mitochondrial respiration: a neglected connection. Cancer Res. 2015;75:3685–6. https://doi.org/10.1158/0008-5472.CAN-15-0491.
62. Orth M, Metzger P, Gerum S, Mayerle J, Schneider G, Belka C, et al. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol. 2019;14:141. https://doi.org/10.1186/s13014-019-1345-6.
63. Azad A, Yin Lim S, D'Costa Z, Jones K, Diana A, Sansom OJ, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy. EMBO Mol Med. 2017;9:167–80. https://doi.org/10.15252/emmm.201606674.
64. Sektioglu IM, Carretero R, Bender N, Bogdan C, Garbi N, Umansky V, et al. Macrophage-derived nitric oxide initiates T-cell diapedesis and tumor rejection. Oncoimmunology. 2016; https://doi.org/10.1080/2162402X.2016.1204506.
65. Molina JR, Sun Y, Protopopova M, Gera S, Bandi M, Bristow C, et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. Nat Med. 2018;24:1036–46. https://doi.org/10.1038/s41591-018-0052-4.
66. Dimcevski G, Kotopoulis S, Bjånes T, Hoem D, Schjøtt J, Gjertsen BT, et al. A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer. J Control Release. 2016;243:172–81. https://doi.org/10.1016/j.jconrel.2016.10.007.
67. Sadeghi-Naini A, Falou O, Hudson JM, Bailey C, Burns PN, Yaffe MJ, et al. Imaging innovations for cancer therapy response monitoring. Imag Med. 2012;4:311–27. https://doi.org/10.2217/iim.12.23.

Chapter 17
The Cachexia Syndrome in Pancreatic Cancer

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Take Home Messages

- Most patients with pancreatic cancer are affected by cancer cachexia.
- Cancer cachexia is associated with increased morbidity and short survival.
- Phenotyping of the cachectic patient is important for adequate risk assessment and tailored treatment.

Pearls and Pitfalls

- Cachexia features should be combined into phenotypes rather than studied separately (e.g. body composition and systemic inflammation).
- Body composition assessment should not be limited to skeletal muscle mass (sarcopenia) but should also include subcutaneous and visceral adipose tissue.
- Pancreatic cancer patients should be tested and treated for pancreatic enzyme deficiency.
- Anti-cachexia treatment should be personalized and multi-modal including nutritional support exercise and pharmacologic treatment.

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Future Perspectives

- The high burden of cancer cachexia in pancreatic cancer and other cancers warrants further development of anti-cachexia treatments.
- Identifying specific mediators of cachexia is vital for developing anti-cachexia treatments.
- Less-invasive tracer techniques with stable-isotope labeled water creates new opportunities for researching protein metabolism in patients with cancer cachexia.
- Development in app-based devices such as activity trackers can help detecting and studying cancer cachexia in an early stage.

17.1 Introduction

Cancer cachexia is perhaps the most important burden for cancer patients [1]. It is characterized by severe weight and muscle loss, and affects more than 80% of pancreatic cancer patients and more than 50% of colorectal cancer patients [2, 3].

The term "cachexia" comes from the Greek words κακος ("bad") and ʿεξις ("condition").

In Europe, an estimate of one million people suffer from cancer cachexia [4]. The international consensus definition of cancer cachexia is based on weight loss, low muscle mass (sarcopenia), and low body mass index. Several pathophysiological drivers including inflammation, altered protein, glucose, and lipid metabolism, anorexia, malabsorption, and neuro-endocrine changes are thought to underlie the development of cancer cachexia [3, 5]. Cancer cachexia is associated with a mortality rate of up to 80% [4], but it should not be considered merely a terminal illness. Symptoms of cachexia may already occur pre-diagnosis with subtle metabolic changes (e.g. mild systemic inflammation or anorexia) in a so-called pre-cachectic phase [3]. Pre-cachexia can develop into cachexia with clinically evident weight loss with or without muscle and/or adipose tissue loss. Only patients with refractory cachexia can be considered as terminal with a permanently altered metabolism, unresponsiveness to anti-cancer therapy, and a life expectancy of less than 3 months (Fig. 17.1) [3].

A major part of the surgical cancer patients presents—with cachexia or pre-cachexia, but the symptoms and clinical presentation can vary widely [6]. In this context, it is important to consider how one should assess and address cachexia, in order to improve perioperative and oncologic outcomes.

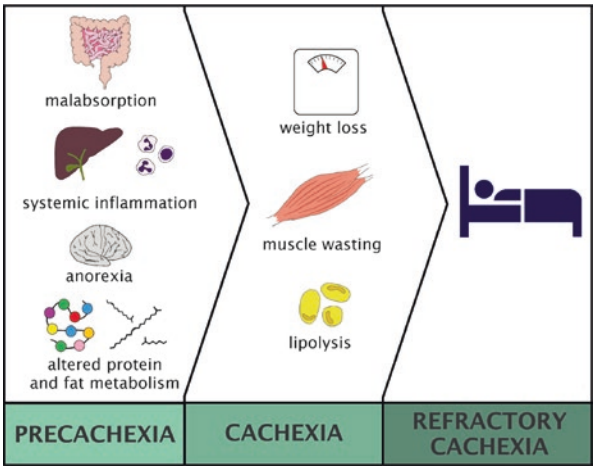

Fig. 17.1 Schematic overview of the different stages of cancer cachexia. *Precachexia* defines a pre-clinical stage in which patients have altered homeostasis without apparent clinical features. Drivers such as malabsorption, systemic inflammation, anorexia, and altered protein and fat metabolism eventually lead to *cachexia* with the classic clinical symptoms of weight loss, muscle wasting and lipolysis. *Refractory cachexia* defines a stage in which the cachectic metabolic changes are irreversible and the patient's life expectancy is less than 3 months. The timeframe in which a patient passes through these stages can vary greatly

17.2 Weight Loss and Body Composition

Weight loss is considered the key symptom of cancer cachexia and, therefore, the main criterion in the international consensus definition of cancer cachexia [3]. Around 85% of patients with pancreatic cancer present with more than 5% weight loss at the time of diagnosis [2, 7]. In contrast, only 14% of patients with metastatic breast cancer present with weight loss at the time of diagnosis [2]. Although weight loss has been reported to have a negative effect on overall survival in pancreatic cancer patients in univariable analysis [2], it is not a risk factor after correction for age, disease stage, and systemic inflammation [8]. This is probably related to differences in the aetiology of weight loss among patients, which can result from reduced food intake and/or increased catabolism [3]. In addition, weight loss does not indicate the tissue types affected: e.g. skeletal muscle, adipose tissue, or other tissues. On top of that, oedema and tumour load can cause an increase in body weight, potentially masking remote tissue loss. While weight loss is a practical and useful indicator of cachexia, a more thorough nutritional assessment is necessary to identify the severity of the metabolic disturbances as well as the underlying mechanisms of cachexia in patients.

Assessing body composition and its changes over time can give valuable information on a patient's cachectic state. Body composition can be assessed using several methods including dual-energy X-ray absorptiometry, bioelectrical impedance

analysis, computed tomography (CT) scanning, and magnetic resonance scanning. Recent progress in CT analysis allows for relatively easy body composition assessment using a single CT-image [9]. By measuring the total area of skeletal muscle (SM), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) at the level of the third lumbar vertebra and adjusting it for patient height, accurate estimations of total body mass and composition can be made (L3-index) [9]. CT-based body composition analysis offers an important advantage over the simple assessment of body weight. It can differentiate between different types of tissues and it is not influenced by oedema, ascites, or tumour load (in contrast to other methods such as bioelectrical impedance analysis) [10]. As CT-scans are usually available of patients with cancer, this approach has been used in a large number of studies including surgical hepato-pancreato-biliary (HPB) cancer patients. Alternatively, magnetic resonance imaging can also be used for body composition assessment using a similar approach [11, 12]. In pancreatic (cancer) surgery, low skeletal muscle mass (i.e. sarcopenia) has been reported to be associated with increased postoperative complications and operative mortality in some studies [13–15]. However, other studies did not find an association between low skeletal muscle mass and long-term outcome, specifically overall survival, in pancreatic cancer patients [14, 16], indicating that additional factors might have an important impact on overall survival in these patients. Low skeletal muscle mass has also been associated with increased postoperative complications [16], specifically with the development of post-operative anastomotic pancreatic fistula [17].

17.3 Adipose Tissue and Myosteatosis

Loss of adipose tissue in cancer cachexia results primarily from increased lipolysis [18] and can happen earlier than loss of skeletal muscle tissue [19]. Low adipose tissue mass is associated with worse survival in cancer patients. Ebadi et al. found that in a cohort of 1746 cancer patients, a low SAT L3-index was independently associated with poor survival [20]. Moreover, in the presence of sarcopenia, patients with a high SAT L3-index had the longest survival. Furthermore, Choe et al. reported that patients with colorectal cancer who had an increase in VAT after surgery had better overall survival [21]. Large amounts of adipose tissue (in particular visceral adipose tissue) can also have a negative impact on short-term postoperative outcome in surgical patients. In pancreatic cancer, high amounts of VAT have been reported to be associated with higher incidence of major complications [22, 23] and pancreatic fistula [24, 25]. In addition, combinations of risk factors can have additive adverse effects on outcome. For example, patients with pancreatic cancer and a low muscle mass combined with obesity had a shorter survival compared with patients with only a low muscle mass or only obesity [26].

Next to tissue area, CT-based analyses (Fig. 17.2) can provide additional information on certain tissue characteristics. For example, the radiation attenuation or radiodensity of a specific tissue (calculated as the average Hounsfield units of the total tissue area at the L3-level) reflects tissue fat content; in the case of skeletal muscle, this is referred to as “myosteatosis” [27]. The (sub)cellular distribution of

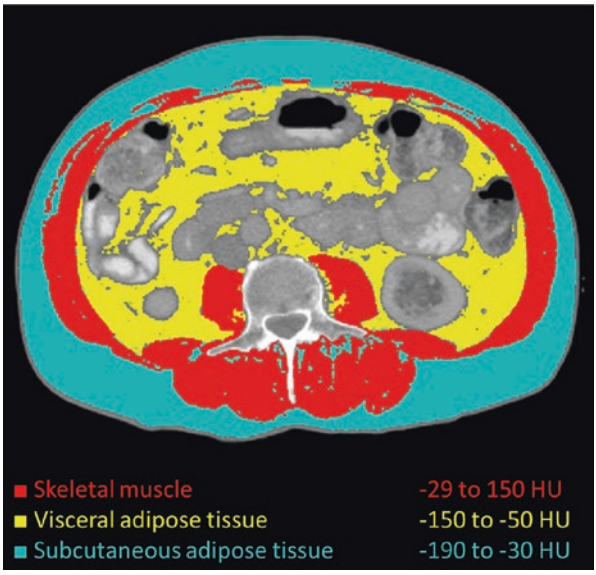

Fig. 17.2 CT-scan body composition analysis. A single CT-slice at the level of the third lumbal vertebra. Tissue areas of skeletal muscle (red), visceral adipose tissue (yellow), and subcutaneous adipose tissue (blue) are annotated using predefined Hounsfield unit (HU) ranges

myosteatosis and potential relationship with muscle quality are still unknown. Nevertheless, the phenomenon of myosteatosis has already been reported in many types of cancer. There is a strong relationship between low muscle radiation attenuation (indicating myosteatosis) and short survival in surgical patients with pancreatic [13, 23] as well as periampullary cancer [23, 28]. As a relatively new parameter, muscle radiation attenuation shows potential for clinical diagnostics. Its relationship to the pathophysiology of cancer cachexia should be further explored, next to the association between muscle radiation attenuation and characteristics of other tissues such as visceral and subcutaneous adipose tissue or the liver. A key question in this context is whether tissue mass and radiation attenuation reflect physical fitness. Low skeletal muscle radiation attenuation, in particular, has often been considered to be an indicator of "poor muscle quality" without support by any functional assessment. A recent article studied the relationship between CT body composition variables and physical fitness, as assessed by cardiopulmonary exercise testing (CPET), in a cohort of patients undergoing hepatopancreatobiliary surgery [29]. In these patients, skeletal muscle radiation attenuation and not skeletal muscle mass correlated well with weight-corrected $\dot{V}O_2$ at anabolic threshold and peak $\dot{V}O_2$. In multivariate linear regression (corrected for age), skeletal muscle radiation attenuation had the strongest association with $\dot{V}O_2$ at anabolic threshold and peak $\dot{V}O_2$. This might indicate that myosteatosis is associated with poor physical fitness while sarcopenia is not. While this seems surprising, skeletal muscle mass assessed at a single timepoint is affected by age, sex, race, build, as well as certain diseases, and might therefore not accurately reflect muscle strength and/or function [30]. For example, Asians generally have lower skeletal muscle mass than Caucasians, but the cut-off for sarcopenia (and related risks) is also lower [31]. Muscle mass does not equal muscle strength. In body-builders with hypertrophic muscles, muscle fibre cross-sectional area was 88% bigger than in control subjects while the muscle fibre peak power was similar [32]. Muscle fibres of athletes had a 58% higher peak power

compared with those of body-builders, while having 67% smaller cross-sectional fibre area. This difference in muscle strength might be related to a lower muscle fibre density in hypertrophic muscle and increased content of non-contractile elements. In disease, low skeletal muscle radiodensity is usually attributed to myosteatosis. Myosteatosis is generally considered the result of a pathologic process involving systemic inflammation and insulin resistance in disease states such as cancer cachexia or obesity [27]. Skeletal muscle insulin resistance and oxidative stress due to β-oxidation might result in decreased glucose uptake, mitochondrial dysfunction, and muscle atrophy [33], possibly leading to decreased muscle function and fitness.

Importantly, studies on body composition usually rely on a single CT-scan of each patient. This generates a snapshot of the patient's body composition while dynamic changes in body composition—certainly in the light of cachexia—could provide much more valuable information. Indeed, analysis of multiple CT-scans over time in patients with colon cancer [34] and ovarian cancer [35] during chemotherapy showed a strong relationship between skeletal muscle loss and survival, whereas there was no or little association between baseline skeletal muscle mass and survival. Unfortunately, studies reporting repeated CT-scan analysis of pancreatic cancer patients are not available to date. Nevertheless, utilizing all available CT-scans in cancer patients should be encouraged in future studies to assess the impact of skeletal muscle loss and adipose tissue loss.

17.4 Systemic Inflammation

Cancer cachexia is often accompanied by inflammation. Patients may have elevated levels of interleukin-1 (IL-1), IL-6, and TNF-alpha, and show an ongoing acute phase response which is clinically apparent by elevated serum C-reactive protein (CRP) and reduced albumin levels [36]. This inflammatory state contributes to activation of pro-catabolic pathways that promote muscle wasting and lipolysis [37]. Elevated CRP levels have been associated with increased resting energy expenditure and increased whole-body protein turnover [38]. Pancreatic cancer patients with elevated CRP levels were shown to have a strongly reduced survival compared with patients without signs of an ongoing acute phase response [8, 39]. In one study, elevated preoperative CRP was associated with an increase in postoperative infectious complications [40]. Whereas both CRP and albumin levels can be used to assess the acute phase response, CRP is consistently the strongest predictor for survival in patients with HPB cancer [8, 41, 42]. The most commonly used cut-off level for increased serum CRP in these studies is >10 mg/L, which is considerably lower than the cut-off used to detect infections [43]. As survival differs between patients with elevated CRP plus normal albumin and patients with both elevated CRP and lowered albumin, preferably both CRP and albumin levels should be used to predict cancer survival (modified Glasgow Prognostic Score) [44]. The complex multifactorial pathogenesis of cancer cachexia warrants further characterisation of different patient phenotypes within the (pre)cachexia spectrum. To this end, (CT-)body

composition features should be stratified for systemic inflammation (elevated serum CRP). In a recent study in patients with colorectal liver metastases, of the patients with elevated serum CRP, 76% also had a low skeletal muscle mass and/or low visceral adipose tissue mass [45]. Interestingly, 49% of patients with low skeletal muscle mass and/or low visceral adipose tissue mass did not show elevated serum CRP levels. Therefore, it seems that these body composition phenotypes can exist independently from systemic inflammation and that systemic inflammation can occur in the absence of a typical "cachectic" body composition phenotype. In fact, systemic inflammation could also be related to an obese phenotype with increased circulating adipokines [46]. Prognostically, patients with both inflammation and low skeletal muscle mass/low visceral adipose tissue mass had an especially short overall survival. This was independent of the Fong prognostic score, which is primarily a function of tumor biology [47]. Similar findings were reported by Dolan et al. in a cohort of operable colorectal cancer patients in which poor survival was primarily associated with the combination of systemic inflammation and a low skeletal muscle index. No data is available for patients with pancreatic cancer. These two studies illustrate the complexity of different phenotypes of patients with cancer and the importance of proper characterization of multiple integrated host characteristics instead of assessing single manifestations of cancer cachexia (e.g. only sarcopenia, only CRP).

17.5 Malabsorption and Altered Protein Metabolism

Malabsorption and maldigestion are major drivers of weight loss in patients with cancer, particularly in those with pancreatic cancer and upper gastro-intestinal cancer. Dysphagia and motility problems often occur in patients with upper gastrointestinal cancer [48], but are also found in patients with non-gastrointestinal cancers like non-small cell lung carcinoma [49]. Forty to 60% of patients with pancreatic cancer suffer from exocrine pancreatic insufficiency preoperatively, which is caused by blockage of the pancreatic duct by the tumour and destruction of acinar cells [50–54]. Blockage of bile flow also contributes to malabsorption by affecting lipid emulsification, which can also occur in patients with tumours of the proximal bile duct or liver hilum. After pancreatic surgery for cancer, the percentage of patients with exocrine insufficiency increases towards 74–100% [53, 55]. Interestingly, exocrine insufficiency has been shown to be associated with a low muscle mass [56] and loss of white adipose tissue (in mice) [57], indicating that it contributes to wasting in pancreatic cancer cachexia. Pancreatic enzyme replacement therapy might offer adequate support [58], but the impact of the method of administration has been poorly studied in pancreatic cancer patients. While the commonly used enteric coated granules are effective in other diseases, the relatively more acidic environment in the duodenum and jejunum of pancreatic cancer patients [59] causes the granules to start releasing enzymes later in the intestine, making them less effective [60]. A more effective approach might be to co-administer uncoated pancreatic enzymes with a proton-pump inhibitor to limit enzymatic degradation in the stomach.

In patients with cancer cachexia, there is an imbalance in protein kinetics with either increased catabolism, decreased anabolism, or both, leading to net protein loss [18, 36, 61, 62]. Cancer cachexia is usually unresponsive to regularly-used nutritional support, a phenomenon called “anabolic resistance” [3, 5]. This lack of response indicates that nutrient handling and especially protein metabolism is altered in cachectic patients. This might be due to failing protein synthesis, increased protein breakdown, or a reprioritisation of protein and amino acids away from peripheral tissues (muscle) towards increased production of acute phase proteins or tumour proteins [18, 36, 61, 62]. In cachectic pancreatic cancer patients with an acute phase response, albumin synthesis rates [63] were shown to be normal whereas fibrinogen synthesis rates were increased, particularly after feeding [64], supporting the theory of reprioritisation.

To study protein metabolism in vivo, amino-acids labelled with a stable isotope (e.g. ^{13}C, a carbon atom containing one extra neutron) are administered to patients orally, parenterally, or both. As the natural availability of stable isotopes is very low, these amino acids are “marked” and can be detected in blood- and tissue samples with mass spectrometry. The ratio between the labelled amino acid and non-labelled amino acid (tracer/tracee ratio) can then be used to calculate protein turnover, synthesis, and sometimes breakdown. A stable isotope tracer study using labelled phenylalanine and tyrosine found that compared with non-oncologic controls, patients with cancer cachexia had markedly increased basal whole-body protein turnover which correlated well with serum CRP-levels [65]. After starting an oral protein drink sip feed, both patient groups achieved a similar net protein balance, meaning that both groups had a similar anabolic response to sip feeding. Thus, the formerly common assumption that patients with cancer cachexia have acquired an anabolic resistance [5] is incorrect on a whole-body protein level. Potentially, the anabolic response may be stimulated further by using a protein bolus instead of sip feed. It has been reported that in healthy elderly subjects, a high protein load is needed (35 g) to generate an anabolic response [66]. However, it must be noted that the anabolic response among different tissues could potentially vary greatly. For example, the measured whole-body anabolic response in cachectic patients may be fully generated by immune cells and tumour tissue, while skeletal muscle tissue and organs may not show any anabolic response.

While there is a vast amount of literature on skeletal muscle protein synthesis in health and disease [67], data on organ tissue and tumour tissue protein turnover is extremely limited. A recent tracer study using peroperative intravenous labelled phenylalanine in patients with resectable pancreatic cancer demonstrated that organ and tumour tissue protein synthesis rates exceeded muscle protein synthesis rates by far (up to 20-fold higher) and, as such, have the potential to strongly influence whole body protein metabolism. Interestingly, pancreatic tumour protein synthesis rates were 2.5-fold lower compared with protein synthesis rates of surrounding non-tumourous pancreatic tissue.

Considering the small size of pancreatic tumours (usually ~2 cm in diameter [68]) and their comparatively low protein synthesis rates, pancreatic tumour cell protein turnover is unlikely to contribute substantially to whole-body protein

metabolism and are, therefore, unlikely to be a major driver of protein loss in cancer cachexia. However, in patients with advanced unresectable pancreatic cancer with metastases, the tumour load could eventually increase to a mass that may significantly affect whole-body protein synthesis.

17.6 Anorexia

Anorexia is common in patients with cancer cachexia, usually presenting as early satiety [18]. It is often observed in jaundiced pancreatic cancer patients with bile duct obstruction, and leads to poor nutritional intake. Stenting of the bile duct usually relieves jaundice and anorexia symptoms [69]. However, in patients with pancreatic cancer, anorexia can persist even after adequate treatment of bile duct obstruction. It has been proposed that increased levels of pro-inflammatory cytokines as a result of an acute phase response may underlie these anorexia-related symptoms [70]. Increased plasma levels of IL-1 have also been reported to be associated with an imbalance between orexigenic hormones such as neuropeptide Y and anorexigenic hormones such as pro-opiomelanocortin, although most evidence is based on animal studies only [71].

17.7 Future Perspectives and Treatment Options

Cancer cachexia is a complex clinical syndrome that can be difficult to identify, quantify, and characterize. The cancer cachexia consensus definition of 2011 describes cancer cachexia as a syndrome of weight loss with loss of skeletal muscle as a key feature [3]. Other features such as anorexia, systemic inflammation, protein metabolism, malnutrition, and psychosocial factors can play (important) roles but might not be present in every patient.

17.7.1 Early Identification

In precachectic patients, in which clinically apparent symptoms such as body weight or muscle loss are usually not (yet) visible, identification of early signs of cachexia can be particularly difficult. On top of that, different combinations of body composition features appear to have different impacts on prognosis. It seems clear that the 2011 cancer cachexia consensus definition of >5% weight loss or >2% weight loss combined with sarcopenia or low BMI is not comprehensive enough for defining such a complex syndrome.

Future definitions should focus on identifying different patient phenotypes within the cancer cachexia spectrum, including all major features of cachexia (i.e.

body composition alterations, inflammation, anorexia, malnutrition and malabsorption, and psychosocial factors). Perhaps these should be cancer-type-specific as some features may have a different impact depending on the cancer type.

17.7.2 Dynamic Investigation

As cancer cachexia is a dynamic process that can pass through several stages, multiple body composition assessments over time are likely to provide more valuable information on the degree and rate of development of cachexia as well as its pathogenesis. Ideally, general practitioners referring patients for diagnosis and treatment for cancer should be involved in cachexia research to identify cachexia and monitor its progression as early as possible. Cheap and quick body composition analysis tools such as bioelectrical impedance devices could be helpful in providing longitudinal data and early detection of changes in body composition in a primary care setting [10]. Novel tools such as applications for smartphones, activity trackers, and internet connected weight scales could even be employed for simple daily assessments.

17.7.3 Pre- and Post-treatment Assessments

Assessments during and after treatment should also be performed as cachexia-related phenotypes can change quickly. The patient with pancreatic cancer and biliary obstruction is a good example. These patients can lose a considerable amount of weight within a couple of weeks. However, after endoscopic stenting of the common bile duct, some patients stop losing weight or even start gaining weight again. In this case, the sustained weight loss is primarily attributed to malabsorption and maldigestion due to mechanical blockage of bile flow and pancreatic juice (containing enzymes) or the cholestasis per se. Such a patient will differ in cachexia phenotype from a weight losing pancreatic cancer patient without biliary obstruction and with elevated CRP levels. In the latter patient, weight loss is likely to be primarily attributable to a catabolic state driven by inflammation and altered metabolism, and possibly has a different (worse) prognosis.

17.7.4 Inputs from Translational Research

Primary human tumour organoid [72] cultures obtained from cachectic and non-cachectic patients could provide a good platform for identifying cachexia-inducing mediators produced by tumour cells and their mechanisms of action. These systems could subsequently also be used to evaluate efficacy of therapeutic anti-cachectic

agents. However, the complex interplay between tumour cells, immune cells, organs, skeletal muscle, and adipose tissue can probably never be mimicked in vitro, stressing the importance of in vivo studies with extensive sampling of blood and tissue biopsies.

17.7.5 A Multimodal Approach

Cancer cachexia cannot be treated with a single targeted therapy but should be addressed using a multimodal approach, including at least nutritional support, anti-inflammatory drugs and/or immunonutrition, and exercise [5]. However, three major steps have to be made before such therapy could be effectively implemented (Fig. 17.3). Firstly, there should be more awareness and knowledge about cancer cachexia among clinicians treating patients with (pancreatic) cancer. While the research field of cancer cachexia is rapidly growing, many clinicians are still unaware of the syndrome and its many manifestations. The term cachexia is often

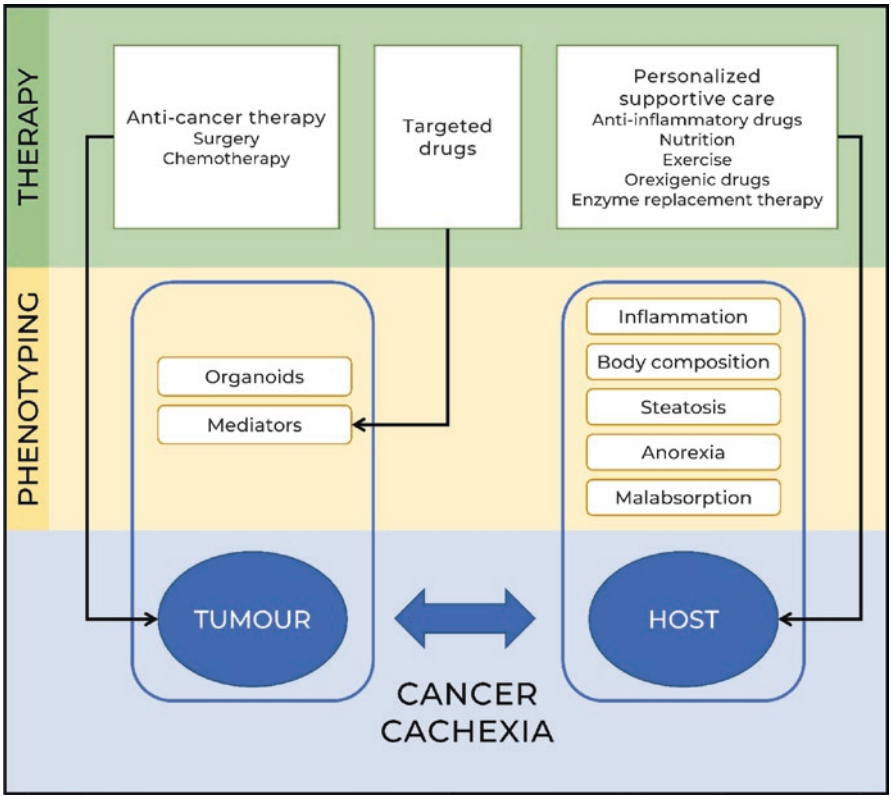

Fig. 17.3 Clinical approach to cancer cachexia

still reserved for severely malnourished weight-losing patients. As anti-cachectic therapy should be started as early as possible, clinicians should be informed on the different indicators of (pre)cachexia and screening for (pre)cachexia should be implemented into diagnostic oncology guidelines. Secondly, many clinical (especially surgical) prehabilitation programmes aim to improve the patient's physical condition before treatment (e.g. nutrition and exercise 6 weeks prior to surgery) to reduce treatment related complications. While this may be beneficial in non-oncologic patients, in cancer patients such strategies have proven to be ineffective in improving the patient's body composition and long term outcome (i.e. overall survival) [73, 74]. Thus, whereas these strategies may improve surgical outcome (e.g. complication rate), it is questionable if they can improve oncologic outcome.

Possibly, prehabilitation programmes fail to achieve substantial benefits because the cancer remains untreated (and metabolically active) during prehabilitation. An alternative approach would be to combine anti-cachectic therapy with oncologic treatment and remove the cause (i.e. the tumour) as quickly as possible after diagnosis, thereby eliminating catabolic drivers, and continue anti-cachectic therapy after surgery. Clinical trials are needed to support this concept.

17.7.6 Drugs Targeting Cachexia Mechanisms

Finally, a true breakthrough in the treatment of cachexia would be the development of a drug targeting specific cachexia drivers and/or mechanisms. Obviously, these mediators will have to be defined first, again stressing the importance of fundamental research on tumour-derived mediators. A specific anti-cachexia drug would ideally be given in a (neo)adjuvant setting and could potentially improve survival, morbidity, and quality of life in both curative and palliative patients with cancer.

17.8 Conclusion

Cancer cachexia is a highly prevalent syndrome among patients with pancreatic cancer and significantly affects morbidity and overall survival. As different combinations of cachexia related symptoms exist, thorough screening is important and should include body composition, nutritional status, physical fitness, inflammatory status, and malabsorption. Treatment should start as early as possible with a personalized and multi-modal approach.

References

1. Mann CD, Palser T, Briggs CD, et al. A review of factors predicting perioperative death and early outcome in hepatopancreaticobiliary cancer surgery. HPB. 2010;12(6):380–8.
2. Dewys W, Begg C, Lavin P, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.

3. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
4. von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers-update. J Cachexia Sarcopenia Muscle. 2014;5(4):261–3.
5. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90–9.
6. Lodewick TM, van Nijnatten TJ, van Dam RM, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? HPB. 2015;17(5):438–46.
7. Porta M, Fabregat X, Malats N, et al. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol. 2005;7(5):189–97.
8. Falconer JS, Fearon KC, Ross JA, et al. Acute-phase protein response and survival duration of patients with pancreatic cancer. Cancer. 1995;75(8):2077–82.
9. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.
10. Haverkort EB, Reijven PL, Binnekade JM, et al. Bioelectrical impedance analysis to estimate body composition in surgical and oncological patients: a systematic review. Eur J Clin Nutr. 2015;69(1):3–13.
11. van Dijk DPJ, Bakers FCHB, Sebastian S, et al. Myosteatosis predicts survival after surgery for periampullary cancer: a novel method using MRI. HPB. 2018;20(8):715–20.
12. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333–8.
13. Okumura S, Kaido T, Hamaguchi Y, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. Surgery. 2015;157(6):1088–98.
14. Onesti JK, Wright GP, Kenning SE, et al. Sarcopenia and survival in patients undergoing pancreatic resection. Pancreatology. 2016;16(2):284–9.
15. Peng P, Hyder O, Firoozmand A, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478–86.
16. Joglekar S, Asghar A, Mott SL, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol. 2014;111(6):771–5.
17. Nishida Y, Kato Y, Kudo M, et al. Preoperative sarcopenia strongly influences the risk of postoperative pancreatic fistula formation after pancreaticoduodenectomy. J Gastrointest Surg. 2016;20(9):1586–94.
18. Tisdale M. Mechanisms of cancer cachexia. Physiol Rev. 2009;89(2):381–410.
19. Fouladiun M, Körner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care—correlations with food intake, metabolism, exercise capacity, and hormones. Cancer. 2005;103(10):2189–98.
20. Ebadi M, Martin L, Ghosh S, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. Br J Cancer. 2017;117(1):148–55.
21. Choe EK, Park KJ, Ryoo SB, Moon SH, Oh HK, Han EC. Prognostic impact of changes in adipose tissue areas after colectomy in colorectal cancer patients. J Korean Med Sci. 2016;31(10):1571–8.
22. Sandini M, Bernasconi DP, Fior D, et al. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. Nutrition. 2016;32(11–12):1231–7.
23. van Dijk DP, Bakens MJ, Coolsen MMM, et al. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(2):317–26.
24. Tranchart H, Gaujoux S, Rebours V, et al. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. Ann Surg. 2012;256(1):139–45.
25. Pecorelli N, Carrara G, De Cobelli F, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. Br J Surg. 2016;103(4):434–42.

26. Tan B, Birdsell L, Martin L, Baracos V, Fearon K. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973–9.
27. Aubrey J, Esfandiari N, Baracos VE, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014;210(3):489–97.
28. van Rijssen LB, van Huijgevoort NC, Coelen RJ, et al. Skeletal muscle quality is associated with worse survival after pancreatoduodenectomy for periampullary, nonpancreatic cancer. Ann Surg Oncol. 2017;24(1):272–80.
29. Malcolm AW, Van Dijk DPJ, Fredrick G, et al. Myosteatosis is associated with poor physical fitness in patients undergoing hepatopancreatobiliary surgery. J Cachexia Sarcopenia Muscle. 2019;10(4):860–71.
30. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. Proc Nutr Soc. 2015;74(4):355–66.
31. Chen L-K, Liu L-K, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15(2):95–101.
32. Meijer JP, Jaspers RT, Rittweger J, et al. Single muscle fibre contractile properties differ between body-builders, power athletes and control subjects. Exp Physiol. 2015;100(11):1331–41.
33. Fukawa T, Yan-Jiang BC, Min-Wen JC, et al. Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. Nat Med. 2016;22(6):666–71.
34. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol. 2016;34(12):1339–44.
35. Rutten IJG, van Dijk DPJ, Kruitwagen RFPM, Beets-Tan RGH, Olde Damink SWM, Van Gorp T. Changes in skeletal muscle mass during neoadjuvant chemotherapy are related to survival in ovarian cancer. J Cachexia Sarcopenia Muscle. 2016;7(4):458–66.
36. Fearon KC, Barber MD, Falconer JS, McMillan DC, Ross JA, Preston T. Pancreatic cancer as a model: inflammatory mediators, acute-phase response, and cancer cachexia. World J Surg. 1999;23(6):584–8.
37. Tisdale MJ. Zinc-alpha2-glycoprotein in cachexia and obesity. Curr Opin Support Palliat Care. 2009;3(4):288–93.
38. Falconer JS, Fearon KC, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. Ann Surg. 1994;219(4):325–31.
39. Pine JK, Fusai KG, Young R, et al. Serum C-reactive protein concentration and the prognosis of ductal adenocarcinoma of the head of pancreas. Eur J Surg Oncol. 2009;35(6):605–10.
40. Neal CP, Mann CD, Garcea G, Briggs CD, Dennison AR, Berry DP. Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases. Arch Surg. 2011;146(4):471–8.
41. Køstner AH, Kersten C, Löwenmark T, et al. The prognostic role of systemic inflammation in patients undergoing resection of colorectal liver metastases: C-reactive protein (CRP) is a strong negative prognostic biomarker. J Surg Oncol. 2016;114(7):895–9.
42. Ishizuka M, Kita J, Shimoda M, et al. Systemic inflammatory response predicts postoperative outcome in patients with liver metastases from colorectal cancer. J Surg Oncol. 2009;100(1):38–42.
43. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med. 1999;17(6):1019–25.
44. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer. 2011;104(4):726–34.
45. van Dijk DPJ, Matthew K, Farshad F, et al. Host phenotype is associated with reduced survival independent of tumour biology in patients with colorectal liver metastases. J Cachexia Sarcopenia Muscle. 2018;10(1):123–30.
46. Graßmann S, Wirsching J, Eichelmann F, Aleksandrova K. Association between peripheral adipokines and inflammation markers: a systematic review and meta-analysis. Obesity. 2017;25(10):1776–85.

47. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309.
48. Cavallin F, Scarpa M, Cagol M, et al. Esophageal cancer clinical presentation. Ann Surg. 2018;267(1):99–104.
49. Vaidya GN, Lutchmansingh D, Paul M, John S. Gastroparesis as the initial presentation of pulmonary adenocarcinoma. BMJ Case Rep. 2014;2014:bcr2014207228.
50. Perez MM, Newcomer AD, Moertel CG, Go VL, Dimagno EP. Assessment of weight loss, food intake, fat metabolism, malabsorption, and treatment of pancreatic insufficiency in pancreatic cancer. Cancer. 1983;52(2):346–52.
51. Ihse I, Arnesjo B, Kugelberg C, Lilja P. Intestinal activities of trypsin, lipase, and phospholipase after a test meal. An evaluation of 474 examinations. Scand J Gastroenterol. 1977;12(6):663–8.
52. Matsumoto J, Traverso LW. Exocrine function following the whipple operation as assessed by stool elastase. J Gastrointest Surg. 2006;10(9):1225–9.
53. Tseng DS, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas. 2016;45(3):325–30.
54. Sikkens ECC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol. 2014;48(5):6.
55. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. Br J Surg. 2014;101(2):109–13.
56. Shintakuya R, Uemura K, Murakami Y, et al. Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease. Pancreatology. 2017;17(1):70–5.
57. Danai LV, Babic A, Rosenthal MH, et al. Altered exocrine function can drive adipose wasting in early pancreatic cancer. Nature. 2018;558(7711):600–4.
58. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998;42(1):92–6.
59. DiMagno EP, Malagelada JR, Vay L, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency—comparison of two dosage schedules. N Engl J Med. 1977;296(23):1318–22.
60. Graham DY. Enzyme replacement therapy of exocrine pancreatic insufficiency in man—relation between in vitro enzyme activities and in vivo potency in commercial pancreatic extracts. N Engl J Med. 1977;296(23):1314–7.
61. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153–66.
62. Hasselgren P, Pedersen P, Sax H, Warner B, Fischer J. Current concepts of protein turnover and amino acid transport in liver and skeletal muscle during sepsis. Arch Surg. 1988;123(8):992–9.
63. Fearon K, Falconer J, Slater C, McMillan D, Ross J, Preston T. Albumin synthesis rates are not decreased in hypoalbuminemic cachectic cancer patients with an ongoing acute-phase protein response. Ann Surg. 1998;227(2):249–54.
64. Preston T, Slater C, McMillan D, Falconer J, Shenkin A, Fearon K. Fibrinogen synthesis is elevated in fasting cancer patients with an acute phase response. J Nutr. 1998;128(8):1355–60.
65. van Dijk DPJ, van de Poll MCG, Moses AGW, et al. Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. J Cachexia Sarcopenia Muscle. 2015;6(3):212–21.
66. Pennings B, Groen B, de Lange A, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. Am J Phys Endocrinol Metab. 2012;302(8):9.
67. Smith GI, Patterson BW, Mittendorfer B. Human muscle protein turnover—why is it so variable? J Appl Physiol. 2011;110(2):480–91.
68. Furukawa H, Iwata R, Moriyama N. Growth rate of pancreatic adenocarcinoma: initial clinical experience. Pancreas. 2001;22(4):366–9.

69. Ballinger AB, McHugh M, Catnach SM, Alstead EM, Clark ML. Symptom relief and quality of life after stenting for malignant bile duct obstruction. Gut. 1994;35(4):467–70.
70. Wigmore SJ, Plester CE, Ross JA, Fearon KC. Contribution of anorexia and hypermetabolism to weight loss in anicteric patients with pancreatic cancer. Br J Surg. 1997;84(2):196–7.
71. Plata-Salamán CR. Central nervous system mechanisms contributing to the cachexia–anorexia syndrome. Nutrition. 2000;16(10):1009–12.
72. Boj Sylvia F, Hwang C-I, Baker Lindsey A, et al. Organoid models of human and mouse ductal pancreatic cancer. Cell. 2015;160(1–2):324–38.
73. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(5):371–85.
74. Fearon KCH, Barber MD, Moses AG, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J Clin Oncol. 2006;24(21):3401–7.

Chapter 18
Role of Stroma in Pancreatic Cancer

Malin Sund

Take Home Messages
- Stroma makes up the bulk of the tumour volume in PDAC.
- Stroma can be both tumour permissive and repressive.
- Stroma affects the delivery and effect of PDAC treatments.
- Stroma can be a source of biomarkers and a therapeutic target.

Pearls and Pitfalls
- Not all stroma is the same.
- There are significant and yet unexplored cues to PDAC biology in the stroma.
- Too many studies performed in small cohorts without external validation.

Future Perspectives
- Establish the molecular traits of a permissive versus repressive stroma.
- Explore how to push PDAC towards a repressive stroma.
- Validate the most promising stromal biomarkers in large and well annotated cohorts and include these in prospective trials on early PDAC.

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18.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense and abundant stroma that makes up the bulk of the tumour volume. Stroma influences tumour progression and is modified by both radiotherapy and systemic therapies given. The stroma by itself also influences the effect of a given therapy, and biomarkers discovered in the stroma carry prognostic and treatment predictive value although not yet translated into clinical practice and decision-making.

Several stromal compartments and structures (vasculature, matrix depletion and immunotherapy) have been evaluated as therapeutic targets with excellent results in experimental models, but none have yet shown a value in the treatment of patients with metastatic disease. No trials have yet been performed in patients with early stage PDAC and stromal targeting.

This chapter will give a brief overview of core elements of stroma and its role in PDAC for cancer biology and potential treatment.

18.2 Definition of the Stroma

The tumour stroma is defined as all the non-malignant cells and extracellular matrix (ECM) of a cancer [1]. Pancreatic cancer and especially pancreatic ductal adenocarcinoma (PDAC) is special in terms of a unique histology whereby the vast majority of the tumour mass (up to 80–90%; Fig. 18.1) is made up of the stroma [2–4].

The stroma contains cellular components such as fibroblasts, immune cells and cells of the vascular system (Fig. 18.2), although the largest portion of the stroma

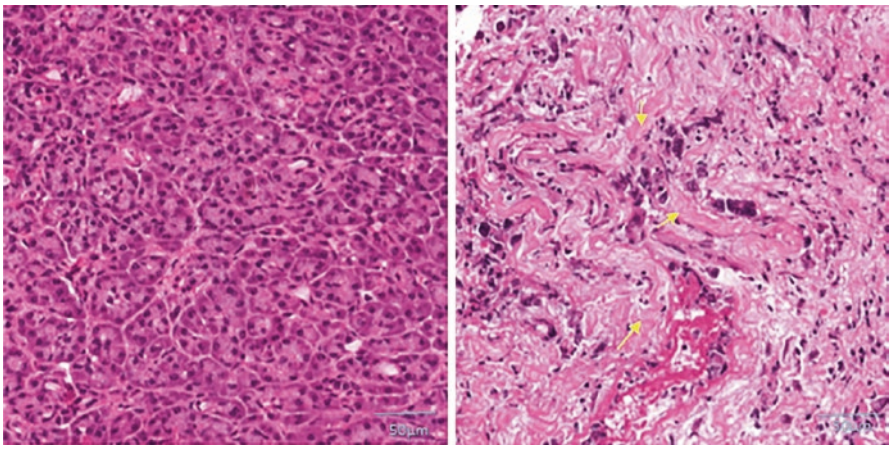

Fig. 18.1 Normal (left) and pancreatic cancer (right) stroma. H&E histology of normal pancreas and a PDAC sample showing an abundant ECM. Development of highly dense fibrotic (desmoplasia) environment around the tumor cells (yellow color arrows) in a poorly differentiated cancer (scale bar 50 μm). (Reproduced from [5]. The figure licensed under the Creative Commons Attribution 4.0 International License)

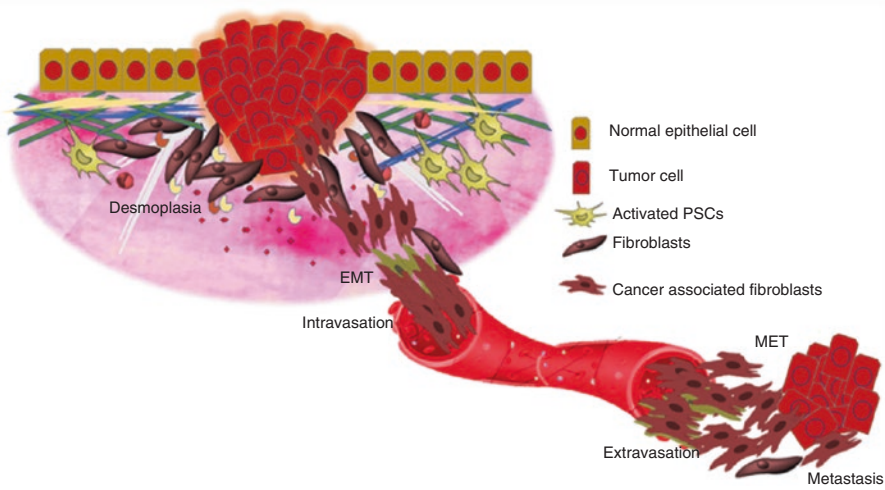

Fig. 18.2 Cancer cell-stromal crosstalk in pancreatic cancer and tissue. Cartoon of cancer cell-stromal interaction. During epithelial-mesenchymal transition (EMT), tumorous epithelial cells undergo various bio-physiological modifications and lose their polarity, detach from the basement membrane and invade the surrounding tissue. The angiogenic switch and tumor vasculature facilitate the intravasation of metastatic tumor cells. The cells that survive in circulation extravasate into distant organ and undergo mesenchymal-to-epithelial (MTE) transition to form tumor colonization. (Reproduced from [5]. The figure licensed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/))

consists of structural ECM proteins such as collagens and proteoglycans such as hyaluronan produced both by the stromal and cancer cells and with effects on tumour progression [1, 6]. Experimental and clinical data using several different types of study set-ups and cohorts have shown the capacity of the stromal compartment to be a driver in tumour progression [5, 7–9].

In the cancer microenvironment, stromal cells become activated and primed by the cancer cells leading both to a changed morphology altered protein expression. Such cells termed as being cancer-associated i.e. cancer-associated fibroblast (CAFs) or tumour-associated macrophages (TAMs) in order to separated them from resident cells of the healthy tissue [1, 10]. CAFs are the major source of the increased level of ECM proteins in the tumour stroma. CAFs can develop from different sources (Fig. 18.3) although the majority likely transdifferentiate from the pancreatic stellate cells and resident fibroblasts, but a portion also develop from bone-marrow derived cells and from epithelial cells through the process of epithelial-to-mesenchymal transformation (EMT) [11–13]. Besides CAFs and the cancer cells also the immune cells take part in modifying the tumour stroma, with the PDAC immune microenvironment being characterized by an exhaustion of cytotoxic T lymphocytes and suppressive immune cell infiltrates that are dominated by macrophages [14].

The stromal reaction, also known as desmoplasia, was initially thought solely to be a defensive mechanism by which the host aims to prevent further tumour growth, and with many similarities to the processes observed in wound healing [1, 15, 16]. It is however currently well established that the stromal reaction in any cancer is

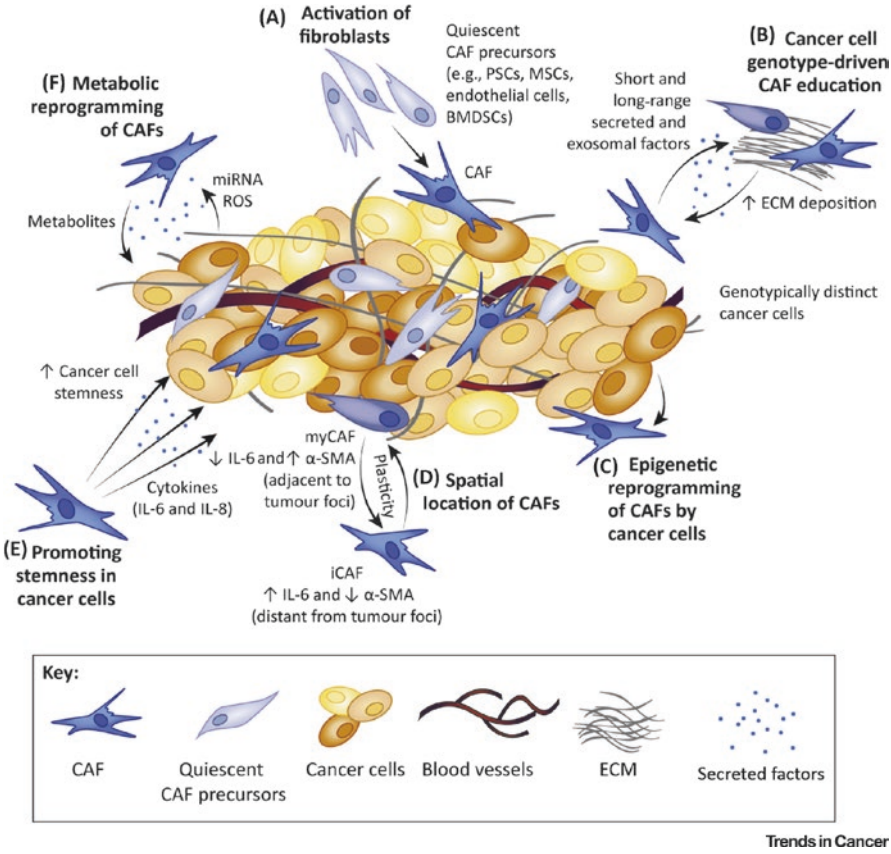

Fig. 18.3 Mechanisms of cancer-associated fibroblast (CAF) heterogeneity. (A) CAFs can originate from several different cell types and, therefore, exhibit a range of activation states that can be further stimulated to alter cancer development. (B) The molecular heterogeneity of cancer cells drives differences in CAF subpopulations via direct, short-, and long-range paracrine signalling. (C) Cancer cells secrete factors that can reprogram the epigenome of CAFs, resulting in more aggressive phenotypes. (D) Varied localisation of CAFs within the tumour microenvironment (TME) leads to differences in the signals that CAFs receive, resulting in functionally and spatially distinct CAF subpopulations. (E) Specific CAF populations can promote a highly plastic, stem cell-like population of cancer cells that can contribute to chemoresistance. (F) Metabolic coupling between CAFs and tumour cells occurs via tumour cell manipulation of distinct CAF subpopulations, where CAFs produce energy-rich metabolites to feed the tumour cells. *α-SMA* alpha smooth muscle actin, *BMDSC* bone marrow-derived stem cell, *ECM* extracellular matrix, *iCAF* inflammatory CAF, *IL-6/8* interleukin 6/8, *MSC* mesenchymal stem cell, *myCAF* myofibroblastic CAF, *PSC* pancreatic stellate cell, *ROS* reactive oxygen species. (Reproduced with permission from Pereira BA, Vennin C, Papanicolaou M, Chambers CR, Herrmann D, Morton JP, Cox TR, Timpson P. CAF Subpopulations: A New Reservoir of Stromal Targets in Pancreatic Cancer. Trends Cancer. 2019 Nov;5(11):724–741)

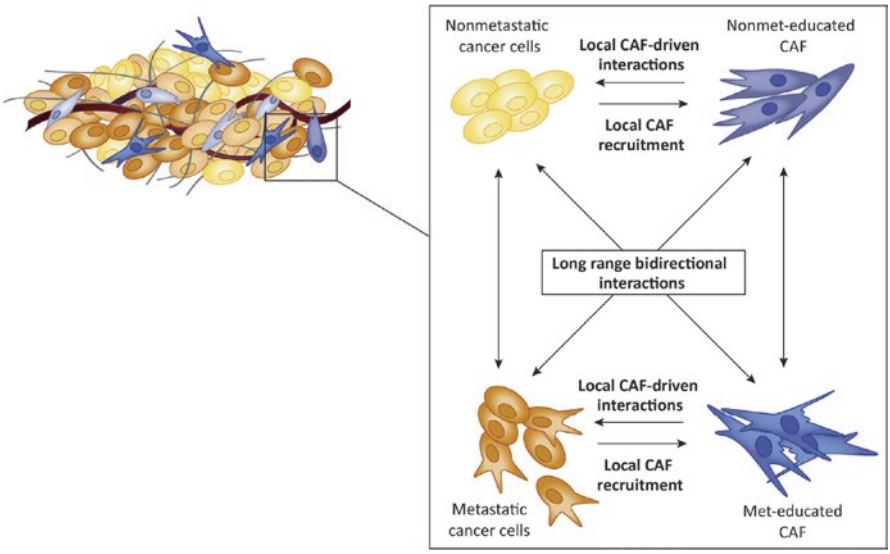

Fig. 18.4 CAF and tumour cell crosstalk can occur through both local and long-range paracrine signalling. Molecularly and phenotypically aggressive cancer cells and CAFs are able to confer protumourigenic characteristics in spatially distinct, less aggressive counterparts through short- and long-range secreted and exosomal factors. *met* metastasis/metastatic. (Reproduced with permission from Pereira BA, Vennin C, Papanicolaou M, Chambers CR, Herrmann D, Morton JP, Cox TR, Timpson P. CAF Subpopulations: A New Reservoir of Stromal Targets in Pancreatic Cancer. Trends Cancer. 2019 Nov;5(11):724–741)

very heterogeneous even within the same tumour, and that depending on these settings the stroma can promote or prevent tumour progression [1]. There is an extensive interplay between CAFs and the cancer cells (Fig. 18.4), which takes place by direct cell-to-cell contact, or indirectly by signalling through various ECM components, growth factors, cytokines and other bioactive substances sequestered within the tumour stroma [1, 5, 7–9, 11]. Moreover, subpopulations of CAFs can have different roles in tumour progression and modulation of the stroma, thus targeting these roles open up for potential new therapeutic targets [17, 18].

18.3 Effect of Stroma on Treatment

Histologically there are relatively scarce number of cancer cells in a sea of stroma in PDAC [2]. How does the stroma affect different PDAC treatments? Most studies have focused on the stroma being a physical barrier that hinders the delivery of therapeutics. The dense ECM combined with a perceived low vascularity raises the intratumoral pressure, leads to poor perfusion and thus hinders sufficient concentrations of therapeutic substances to reach the cancer [4, 9, 19–21]. This increase in pressure is due to local micro-regional interactions between hyaluronic acid (HA)

and collagen in the stroma, whereby blood vessels become closed off due to the swelling of HA combined with the restrictive influence of the collagen matrix and thus results in poor perfusion of drugs [22].

The stroma might however also hinder drug effect by other means than just prevention of delivery. As an example of such it has been shown that both CAFs/stellate cells and macrophages in the tumour microenvironment can release substances that prevent gemcitabine effect [23–25]. The stroma can also confer radioprotection as shown in experimental studies using *in vitro* cultures of pancreatic cancer cells lines with CAFs [26]. Similarly in animal models using xenografted human CAFs and pancreatic cancer cells, the former provided a protection to radiotherapy [27]. Therefore, the stroma affects the treatment in far more intricate ways than merely prevention of drug delivery.

18.4 Effect of Treatment on Stroma

As discussed above the stroma can be a direct barrier of allowing systemic treatments to reach the cancer cells and thus protects the growing tumour and modify the effect of treatments. How do treatments change the stroma with potential effects on tumour progression?

In radiotherapy ionizing radiation is given with the intent to cause cancer cell death, however the same therapy can lead to an 'activated' phenotype that promotes persistent remodelling of the ECM, by increased expression of proteases and growth factors [28]. Studies on preoperative radiotherapy given alone have indicated that irradiated patients have less local recurrences, but more distant metastatic spread compared to non-irradiated patients [29]. Studies using clinical PDAC samples have furthermore shown that radiotherapy stimulates stromal production of ECM proteins thus potentially further enhancing desmoplasia [30]. *In vitro* studies using cultured human tumour-derived pancreatic stellate cells show an activation after exposure to chemoradiotherapy compared to cells before treatment [31]. These results indicate that radiotherapy might modify the stroma, could lead to increased tumour progression and should thus be combined with other treatments such as chemotherapy.

Compared to radiotherapy the effect of chemotherapy on the stromal structure and content is less well studied. Neoadjuvant therapy allows for more of such studies to be performed in clinical materials. Neoadjuvant gemcitabine plus nab-paclitaxel therapy leads to changes of the stroma itself [32] with increased capsulated fibrosis and more of this type of mature fibrosis indicated better outcome [33]. Studies on preoperative radiochemotherapy have shown the same i.e. achieving a strong fibrotic reaction indicates favourable outcome [34]. These findings thus show that stromal remodelling by therapy can change the tumour microenvironment from a cancer supportive to a repressive state and establishing the molecular traits of this mature stroma will be of great interest.

18.5 Stroma as a Source of Biomarkers

The pancreatic cancer field is lacking good and clinically relevant prognostic and treatment predictive biomarkers, both in terms of tissue-based markers as well as circulating tumour markers [35].

Basic morphological/histological analysis of the stroma such as estimating the number of fibrotic foci in haematoxylin & eosin staining has been found to be significantly associated with survival, but although being available on every surgical specimen analysed has not been established as a prognostic marker in the clinic [36, 37].

By analysing the ratio of α-SMA-positive CAFs in the stroma to the collagen deposition an "activated stromal index (ASI)" has been described [38]. The ASI was found to be a negative prognostic marker using tissue samples from resected PDAC specimens, with patients with the lowest activated stromal index having the best prognosis. In multivariable analysis the activated stromal index was found to be an independent prognostic marker comparable to the nodal status of the patient [38]. The negative prognostic value high α-SMA-positivity was subsequently validated using tissue samples from the CONKO-001 randomized controlled trial (RCT) investigating the role of adjuvant gemcitabine as compared with observation after surgery with curative intent. This study showed that high α-SMA-positivity was associated with both reduced disease-free and overall survival [39].

The effect of stroma on tumour progression is captured by the Moffitt grading, whereby the stromal reaction of a PDAC is divided into "normal" and "activated" with an apparent independent effect on prognosis [40]. This is based on gene expression data from PDAC samples in which tumour, stroma, and normal gene expression is separated by a method called *nonnegative matrix factorization* in order to perform a virtual microdissection allowing the identification of cancer cell- and stroma-specific subtypes carrying prognostic and biologic relevance [40]. Patients with an "activated stroma" have both worse median and 1-year survival, when compared to patients with a "normal stroma" subtype (median 15 vs. 24 months and 1-year survival 60 vs. 82%, respectively) [40]. The "normal stroma" of the Moffitt grading is characterized by expression of well-known stellate cells markers including proteins like smooth muscle actin, vimentin and desmin. The "activated stroma" on the other hand displayed a features of an inflammatory response and included markers associated with macrophages (CCL13, CCL18 and ITGAM), proteins related to tumour promotion (*SPARC*, WNT family members, *MMP9* and *MMP11*) and those related to CAFs (FAP) [40]. This "activated stroma" signature was found to be mainly produced by the cells of the stromal compartment with little or none influence by the cancer cells themselves [40].

The expression of structural ECM components, such as collagens, have gained recent interest as biomarkers and have been analysed in PDAC tissue. High collagen fibre alignment is associated with poor prognosis [41], as is high expression of COL6A1 and A3 [42, 43], whereas no prognostic value was observed for stromal COL4 expression [44]. Moreover, matrisome proteins that regulate the ECM

proteins have been extensively studied as biomarkers in PDAC as described in the systematic review by Fiorino et al. [45]. None of these are however routinely included in the histological assessment of PDAC, and there is in general a paucity of biomarker studies conducted in large well-annotated cohorts, and even fewer that have been validated in external cohorts. The other major stromal component hyaluronic acid has been evaluated as a prognostic marker [44, 46] but due to most tumours being highly positive the value is less for prognosis [44]. HA-high tumours appear to respond to stromal depletion therapy by hyaluronan as discussed in Sect. 18.6 below [47].

In terms of circulating biomarkers, the stroma in a cancer undergoes constant remodelling, whereby stromal proteins or parts of structural stromal proteins become released into the circulation [48–51]. These could potentially be used as tumour biomarkers reflecting the tumour volume. Some of the suggested stromal ECM derived circulating biomarkers are fragments from COL1, COL3, COL4, COLA3, COL18 [48, 49, 51, 52] and circulating hyaluronic acid [44, 46]. None of these have however been shown to outperform CA19-9, which is the most widely used circulating tumour marker [53] and is discussed in other chapters of this book. Some studies indicate that combining CA19-9 with a stromal marker might be better than CA 19-9 alone, although as said for the tissue-based markers also these studies need validation in larger datasets [50].

18.6 Stroma as a Specific Treatment Target

The dense stroma has been perceived as one of the causes to the poor effect of systemic treatments in pancreatic cancer and thus modifying the stroma has attracted significant interest [54]. This has been further driven by very promising results of stromal targeting using experimental models [20, 55–60], although conflicting results have also been indicated [61]. Unfortunately, so far stromal targeting has not been equally successful upon translation into clinical trials [62]. Emerging substances targeting the stroma and results from early trials have recently been thoroughly discussed in a systematic review and meta-analysis by van Mecklenbergh et al. [63]. In Table 18.1 the results from RCTs on stromal targets are summarized. Most of these have been tested on a backbone of the most commonly used chemotherapeutic agents such as gemcitabine, nab-paclitaxel and FOLFIRINOX, although some have been tested as monotherapy agents. All RCTs are in patients with advanced disease and mostly in stage IV disease. A lack of effect in such a setting does not necessarily mean that the treatment would not be efficient at earlier disease stages. Neoadjuvant therapy in PDAC is now routine in the borderline resectable PDAC population with on-going trials for upfront resectable disease [64–67]. This might open the chance for also testing agents targeting the stroma in earlier disease stages.

Pancreatic cancer is not considered a well vascularised cancer although this notion is likely due to vessels being compressed, and most anti-angiogenic agents

Table 18.1 Drugs against various targets of stromal components in phase II/III trials

Study agent[a]	Combination agent/ backbone	Phase	Disease stage	No of patients (experimental vs. control)	OS (experimental vs. control)	PFS (experimental vs. control)	Reference
Bevacizumab	Gemcitabine + erlotinib	III	IV	306:301	7.1 vs. 6.0 months, NS	4.6 vs. 3.6 months, p = 0.0002	[68]
Bevacizumab	Gemcitabine	III	LAPC/ IV	302:300	5.8 vs. 5.9 months, NS	3.8 vs. 2.9 months, NS	[73]
Bevacizumab + cetuximab	Gemcitabine (± study agents)	II	LAPC/ IV	30:31	4.2 vs. 5.4 months, NS	1.9 vs. 3.6 months, NS	[70]
Aflibercept	Gemcitabine	III	IV	217:275	6.5 vs. 7.8 months, NS	3.7 vs. 3.7 months, NS	[71]
Axitinib	Gemcitabine	II	LAPC/ IV	103	6.9 vs. 5.6 months, NS	4.2 vs. 3.7 months, NS	[72]
Axitinib	Gemcitabine	III	III/IV	314:316	8.5 vs. 8.3 months, NS	4.4 vs. 4.4 months, NS	[69]
Sorafenib	Gemcitabine (± study agent)	II	IV	15:37	4.3 vs. 6.5 months, NS	2.3 vs. 2.9 months, NS	[74]
Sorafenib	Gemcitabine	III	IV	52:52	8.0 vs. 9.2 months, NS	3.8 vs. 5.7 months, NS	[75]
Sunitinib	None	II	IV	28:27	10.6 vs. 9.2 months, NS	3.2 vs. 2.0 months, p < 0.01	[76]
Sorafenib	Gemcitabine + cisplatin	II	LAPC/ IV	43:44	7.5 vs. 8.3 months, NS	4.3 vs. 4.5 months, NS	[77]
Sunitinib	Gemcitabine	II	LAPC/ IV	54:52	7.6 vs. 9.2 months, NS	2.9 vs. 3.4 months, NS	[78]
Vandetanib	Gemcitabine	II	LAPC/ IV	72:70	8.83 vs. 8.95 months, NS	8.0 vs. 6.1 months, NS	[79]
Vismodegib	Gemcitabine	IIb/II	IV	53:53	6.9 vs. 6.1 months, NS	3.6 vs. 3.8 months, NS	[85]
Cilengitide	Gemcitabine	II	LAPC	46:43	6.7 vs. 7.7 months, NS	4.0 vs. 2.5 months, NS	[86]

(continued)

Table 18.1 (continued)

Study agent[a]	Combination agent/ backbone	Phase	Disease stage	No of patients (experimental vs. control)	OS (experimental vs. control)	PFS (experimental vs. control)	Reference
PEGPH20	Gemcitabine + nab-paclitaxel	II	IV	166:113	Overall 9.6 vs. 9.2 months, NS; HAhigh 11.5 vs. 8.5 months, NS	Overall 6 vs. 5.3 months, p = 0.049; HAhigh 9.2 vs. 5.2 months, p = 0.048	[80]
PEGPH20	FOLFIRINOX	IIb/II	IV	59:55	7.7 vs. 14.4 months	Not available	[47]
BAY 12-9566	Study agent alone vs. gemcitabine	III	IV	138:139	3.7 vs. 6.7 months, p < 0.001	1.7 vs. 3.5 months, p < 0.001	[87]
Masitinib	Gemcitabine	III	LAPC/ IV	172:178	7.7 vs. 7.1 months, NS	Not available	[88]

LAPC locally advanced pancreatic cancer, *OS* overall survival, *PFS* progression free survival

[a]**Stromal targets of the study agent**

Vasculature: Bevacizumab (anti-VEGF antibody (ab)); Cetuximab (anti-EGFR ab); Aflibercept (VEGF-trap); Axitinib (pan-VEGF inhibitor, c-KIT and PDGRF inhibitor); Sorafenib (multi-tyrosine kinase inhibitor (TKI)); Sunitinib (multi-TKI); Vandetanib (multi-TKI); Vismodegib (Hedgehog signalling inhibitor); Cilengitide (αv integrin inhibitor)

Extracellular matrix: PEGPH20 (PEGylated recombinant hyaluronidase)

Cancer cell-Stromal interactions: BAY 12-9566/tanomastat (MMP inhibitor); Masitinib (cKit, PDGFR and FGFR3 inhibitor)

have failed in randomized clinical trials (RCTs) (Table 18.1). These include substances blocking the effect of vascular endothelial growth factor (VEGF), the major pro-angiogenic growth factor in tumours, by agents such as anti-VEGF, VEGF-trap, pan-VEGF inhibitors and inhibitors of VEGF receptor 2 and 3, none of which show an effect on overall survival and progression-free survival [68–75]. Moreover, several multi tyrosine kinase inhibitors (TKIs) that affect tumour vasculature also have failed at RCT stage and having slightly worse estimates than the standard arm, albeit initial promise in preclinical and early clinical settings [63, 76–79] (Table 18.1).

In well-designed experimental studies using models mimicking human pancreatic cancer with a dense hyaluronic acid rich stroma, the depletion of the ECM lead to greatly improved effects of therapy [20, 55]. This was met with excitement and clinical trials using stromal hyaluronic acid depletion by PEGylated recombinant hyaluronidase were initiated in metastatic PDAC on backbones of both nab-Paclitaxel and FOLFIRINOX [47, 80]. Unfortunately, the latter led to a worse outcome than FOLFIRINOX alone and the trial was discontinued. On a nab-Paclitaxel backbone tumours with a high hyaluronan content (HAhigh) were however shown to have an improved progression-free survival (Table 18.1) in a phase II setting [80], and this subgroup of patients (defined as >50% hyaluronan content) was tested further in the phase III HALO-109-301 trial where the first results unfortunately appear not to show any effect although the final results have not yet been published [81].

Another treatment affecting the stroma is immunotherapy where the immune system of the host can be reactivated to clear cancer cells by lifting the immune suppression of the cancer cells by drugs that release the action of check-point inhibitors. Unfortunately, the successes of checkpoint inhibitors and other immune therapies as observed in other cancer types have not been replicated in pancreatic cancer [82, 83].

18.7 Conclusions

Results from clinical trials aiming at targeting the tumours stroma highlight the dual role of the stroma in being both permissive and restrictive in cancer growth. The most recent avenues on targeting the stroma is by trying to establish the actual tumour growth promoting stromal components and signals, and then using these as therapeutic targets i.e. specific subsets of CAFs [18]. Stromal reprogramming, indicating a therapy that changes the stroma from a permissive to a tumour suppressive microenvironment could be a way of using the stroma for treating a PDAC. Understanding the biology of the stroma will undoubtly be one of the keys to increasing the treatment efficacy in PDAC. As pancreatic cancer is becoming increasingly well characterized on a molecular level, the stromal treatment targets will increase. By discovering many such targets more personalized treatment targets will become available as reviewed by Collison et al. [84] and should be accompanied by clinically useful predictive biomarkers.

References

1. Kalluri R, Zeisberg M. Fibroblasts in cancer. Nat Rev Cancer. 2006;6(5):392–401.
2. Verbeke C. Morphological heterogeneity in ductal adenocarcinoma of the pancreas – does it matter? Pancreatology. 2016;16(3):295–301.
3. Neesse A, et al. Stromal biology and therapy in pancreatic cancer. Gut. 2011;60(6):861–8.
4. Kleeff J, et al. Pancreatic cancer microenvironment. Int J Cancer. 2007;121(4):699–705.
5. Thomas D, Radhakrishnan P. Tumor-stromal crosstalk in pancreatic cancer and tissue fibrosis. Mol Cancer. 2019;18(1):14.
6. Tian C, et al. Cancer cell-derived matrisome proteins promote metastasis in pancreatic ductal adenocarcinoma. Cancer Res. 2020;80(7):1461–74.
7. Kadaba R, et al. Imbalance of desmoplastic stromal cell numbers drives aggressive cancer processes. J Pathol. 2013;230(1):107–17.
8. Alexander J, Cukierman E. Stromal dynamic reciprocity in cancer: intricacies of fibroblastic-ECM interactions. Curr Opin Cell Biol. 2016;42:80–93.
9. Piersma B, Hayward MK, Weaver VM. Fibrosis and cancer: a strained relationship. Biochim Biophys Acta Rev Cancer. 1873;2020(2):188356.
10. Mantovani A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;14(7):399–416.
11. Öhlund D, Elyada E, Tuveson D. Fibroblast heterogeneity in the cancer wound. J Exp Med. 2014;211(8):1503–23.
12. Iwano M, et al. Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest. 2002;110(3):341–50.
13. Kidd S, et al. Origins of the tumor microenvironment: quantitative assessment of adipose-derived and bone marrow-derived stroma. PLoS One. 2012;7(2):e30563.
14. Liu X, et al. The reciprocal regulation between host tissue and immune cells in pancreatic ductal adenocarcinoma: new insights and therapeutic implications. Mol Cancer. 2019;18(1):184.
15. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med. 1986;315(26):1650–9.
16. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
17. Öhlund D, et al. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. J Exp Med. 2017;214(3):579–96.
18. Pereira BA, et al. CAF subpopulations: a new reservoir of stromal targets in pancreatic Cancer. Trends Cancer. 2019;5(11):724–41.
19. Hynes RO. The extracellular matrix: not just pretty fibrils. Science. 2009;326(5957):1216–9.
20. Provenzano PP, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(3):418–29.
21. Jacobetz MA, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut. 2013;62(1):112–20.
22. Nieskoski MD, et al. Collagen complexity spatially defines microregions of total tissue pressure in pancreatic cancer. Sci Rep. 2017;7(1):10093.
23. Dalin S, et al. Deoxycytidine release from pancreatic stellate cells promotes gemcitabine resistance. Cancer Res. 2019;79(22):5723–33.
24. Halbrook CJ, et al. Macrophage-released pyrimidines inhibit gemcitabine therapy in pancreatic cancer. Cell Metab. 2019;29(6):1390–1399.e6.
25. Ireland L, et al. Chemoresistance in pancreatic cancer is driven by stroma-derived insulin-like growth factors. Cancer Res. 2016;76(23):6851–63.
26. Mantoni TS, et al. Pancreatic stellate cells radioprotect pancreatic cancer cells through β1-integrin signaling. Cancer Res. 2011;71(10):3453–8.
27. Al-Assar O, et al. Contextual regulation of pancreatic cancer stem cell phenotype and radioresistance by pancreatic stellate cells. Radiother Oncol. 2014;111(2):243–51.
28. Barcellos-Hoff MH, Park C, Wright EG. Radiation and the microenvironment – tumorigenesis and therapy. Nat Rev Cancer. 2005;5(11):867–75.

29. Ishikawa O, et al. Is the long-term survival rate improved by preoperative irradiation prior to Whipple's procedure for adenocarcinoma of the pancreatic head? Arch Surg. 1994;129(10):1075–80.
30. Erkan M, et al. Periostin creates a tumor-supportive microenvironment in the pancreas by sustaining fibrogenic stellate cell activity. Gastroenterology. 2007;132(4):1447–64.
31. Cabrera MC, et al. Human pancreatic cancer-associated stellate cells remain activated after in vivo chemoradiation. Front Oncol. 2014;4:102.
32. Miyashita T, et al. Neoadjuvant chemotherapy with gemcitabine plus nab-paclitaxel reduces the number of cancer-associated fibroblasts through depletion of pancreatic stroma. Anticancer Res. 2018;38(1):337–43.
33. Matsuda Y, et al. Encapsulating fibrosis following neoadjuvant chemotherapy is correlated with outcomes in patients with pancreatic cancer. PLoS One. 2019;14(9):e0222155.
34. Chun YS, et al. Significance of pathologic response to preoperative therapy in pancreatic cancer. Ann Surg Oncol. 2011;18(13):3601–7.
35. Sund M, Kalluri R. Tumor stroma derived biomarkers in cancer. Cancer Metastasis Rev. 2009;28(1–2):177–83.
36. Watanabe I, et al. Advanced pancreatic ductal cancer: fibrotic focus and β-catenin expression correlate with outcome. Pancreas. 2003;26(4):326–33.
37. Couvelard A, et al. Expression of hypoxia-inducible factors is correlated with the presence of a fibrotic focus and angiogenesis in pancreatic ductal adenocarcinomas. Histopathology. 2005;46(6):668–76.
38. Erkan M, et al. The activated stroma index is a novel and independent prognostic marker in pancreatic ductal adenocarcinoma. Clin Gastroenterol Hepatol. 2008;6(10):1155–61.
39. Sinn M, et al. α-Smooth muscle actin expression and desmoplastic stromal reaction in pancreatic cancer: results from the CONKO-001 study. Br J Cancer. 2014;111(10):1917–23.
40. Moffitt RA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47(10):1168–78.
41. Drifka CR, et al. Highly aligned stromal collagen is a negative prognostic factor following pancreatic ductal adenocarcinoma resection. Oncotarget. 2016;7(46):76197–213.
42. Svoronos C, et al. Prognostic value of COL6A3 in pancreatic adenocarcinoma. Ann Hepatobiliary Pancreat Surg. 2020;24(1):52–6.
43. Owusu-Ansah KG, et al. COL6A1 promotes metastasis and predicts poor prognosis in patients with pancreatic cancer. Int J Oncol. 2019;55(2):391–404.
44. Franklin O, et al. *Novel prognostic markers within the CD44-stromal ligand network in pancreatic cancer.* The journal of pathology. Clin Res. 2019;5(2):130–41.
45. Fiorino S, et al. Matricellular proteins and survival in patients with pancreatic cancer: a systematic review. Pancreatology. 2018;18(1):122–32.
46. Cheng X-B, et al. Prognostic impact of hyaluronan and its regulators in pancreatic ductal adenocarcinoma. PLoS One. 2013;8(11):e80765.
47. Ramanathan RK, et al. Phase IB/II randomized study of FOLFIRINOX plus Pegylated recombinant human hyaluronidase versus FOLFIRINOX alone in patients with metastatic pancreatic adenocarcinoma: SWOG S1313. J Clin Oncol. 2019;37(13):1062–9.
48. Willumsen N, et al. Collagen fragments quantified in serum as measures of desmoplasia associate with survival outcome in patients with advanced pancreatic cancer. Sci Rep. 2019;9(1):19761.
49. Ohlund D, et al. Type IV collagen is a tumour stroma-derived biomarker for pancreas cancer. Br J Cancer. 2009;101(1):91–7.
50. Franklin O, et al. Combining conventional and stroma-derived tumour markers in pancreatic ductal adenocarcinoma. Cancer Biomark. 2015;15(1):1–10.
51. Ohlund D, et al. Expression pattern and circulating levels of endostatin in patients with pancreas cancer. Int J Cancer. 2008;122(12):2805–10.
52. Kang CY, et al. Clinical significance of serum COL6A3 in pancreatic ductal adenocarcinoma. J Gastrointest Surg. 2014;18(1):7–15.

53. Humphris JL, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol. 2012;23(7):1713–22.
54. Vennin C, et al. Reshaping the tumor stroma for treatment of pancreatic cancer. Gastroenterology. 2018;154(4):820–38.
55. Olive KP, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009;324(5933):1457–61.
56. Strand MF, et al. A novel synthetic smoothened antagonist transiently inhibits pancreatic adenocarcinoma xenografts in a mouse model. PLoS One. 2011;6(6):e19904.
57. Neesse A, et al. CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer. Proc Natl Acad Sci U S A. 2013;110(30):12325–30.
58. Joensson P, et al. A novel antiangiogenic approach for adjuvant therapy of pancreatic carcinoma. Langenbeck's Arch Surg. 2011;396(4):535–41.
59. Casneuf VF, et al. Antiangiogenic versus cytotoxic therapeutic approaches in a mouse model of pancreatic cancer: an experimental study with a multitarget tyrosine kinase inhibitor (sunitinib), gemcitabine and radiotherapy. Oncol Rep. 2009;22(1):105–13.
60. Li X, et al. Parallel accumulation of tumor Hyaluronan, collagen, and other drivers of tumor progression. Clin Cancer Res. 2018;24(19):4798–807.
61. Özdemir BC, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell. 2014;25(6):719–34.
62. Bijlsma MF, van Laarhoven HWM. The conflicting roles of tumor stroma in pancreatic cancer and their contribution to the failure of clinical trials: a systematic review and critical appraisal. Cancer Metastasis Rev. 2015;34(1):97–114.
63. van Mackelenbergh MG, et al. Clinical trials targeting the stroma in pancreatic cancer: a systematic review and meta-analysis. Cancers. 2019;11(5):588.
64. Ettrich TJ, et al. Neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer - the NEONAX trial (AIO-PAK-0313), a prospective, randomized, controlled, phase II study of the AIO pancreatic cancer group. BMC Cancer. 2018;18(1):1298.
65. Labori KJ, et al. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. BMC Surg. 2017;17(1):94.
66. Ye M, et al. Neoadjuvant chemotherapy for primary resectable pancreatic cancer: a systematic review and meta-analysis. HPB. 2020;22(6):821–32.
67. Heinrich S, et al. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). BMC Cancer. 2011;11:346.
68. Van Cutsem E, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol. 2009;27(13):2231–7.
69. Kindler HL, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol. 2011;12(3):256–62.
70. Ko AH, et al. A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. Investig New Drugs. 2012;30(4):1597–606.
71. Rougier P, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer. 2013;49(12):2633–42.
72. Spano J-P, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. Lancet. 2008;371(9630):2101–8.

73. Kindler HL, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic Cancer: phase III trial of the cancer and leukemia group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617–22.
74. El-Khoueiry AB, et al. A randomized phase II of gemcitabine and sorafenib versus sorafenib alone in patients with metastatic pancreatic cancer. Investig New Drugs. 2012;30(3):1175–83.
75. Gonçalves A, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. Ann Oncol. 2012;23(11):2799–805.
76. Reni M, et al. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: a phase II randomised trial. Eur J Cancer. 2013;49(17):3609–15.
77. Cascinu S, et al. Sorafenib does not improve efficacy of chemotherapy in advanced pancreatic cancer: a GISCAD randomized phase II study. Dig Liver Dis. 2014;46(2):182–6.
78. Bergmann L, et al. A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. Eur J Cancer. 2015;51(1):27–36.
79. Middleton G, et al. Vandetanib plus gemcitabine versus placebo plus gemcitabine in locally advanced or metastatic pancreatic carcinoma (ViP): a prospective, randomised, double-blind, multicentre phase 2 trial. Lancet Oncol. 2017;18(4):486–99.
80. Hingorani SR, et al. HALO 202: randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J Clin Oncol. 2018;36(4):359–66.
81. Tempero MA, et al. HALO 109-301: a randomized, double-blind, placebo-controlled, phase 3 study of pegvorhyaluronidase alfa (PEGPH20) + nab-paclitaxel/gemcitabine (AG) in patients (pts) with previously untreated hyaluronan (HA)-high metastatic pancreatic ductal adenocarcinoma (mPDA). J Clin Oncol. 2020;38(4_suppl):638.
82. Brahmer JR, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65.
83. Royal RE, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33(8):828–33.
84. Collisson EA, et al. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019;16(4):207–20.
85. Catenacci DVT, et al. Randomized phase Ib/II study of gemcitabine plus placebo or Vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J Clin Oncol. 2015;33(36):4284–92.
86. Friess H, et al. A randomized multi-center phase II trial of the angiogenesis inhibitor Cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. BMC Cancer. 2006;6(1):285.
87. Moore MJ, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(17):3296–302.
88. Deplanque G, et al. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. Ann Oncol. 2015;26(6):1194–200.

Chapter 19
Role of the Microbiome in Pancreatic Cancer

Saba Kurtom, Vrishketan Sethi, and Vikas Dudeja

Take Home Messages

- The human microbiome is capable of evolving and changing based on multiple factors including disease states.
- Multiple studies have demonstrated the link between oral, gut and intratumoral bacteria in pancreatic cancer.
- Murine models have demonstrated that eradication of the gut microbiome can lead decrease in tumor progression in pancreatic cancer.
- Inflammatory states—such as pancreatitis and obesity—lead to microbial dysbiosis, leading to increase in bacterial dislocation which may manifest in a downstream immunosuppressive response, increasing the risk of pancreatic cancer progression.

Pearls and Pitfalls

- While 16s rRNA is widely accepted as a technique for bacterial identification, it can be limited in its utility (i.e., several bacterial species have more than one copy of the gene, leading to artificial overrepresentation in the data).
- Studies evaluating the microbiome must be done precisely, particularly when considering sample handling/collecting and analysis of data.
- Variations in the microbiome as well as the surrounding environment can account for discordant results in experiments performed in different laboratories.

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Future Perspectives

- The precise mechanism through which the gut microbiome modulates tumor-specific immunity remains unclear.
- How microbes and their associated ligands, exotoxins, and endotoxins manipulate pancreatic cancer immunity could potentially become a target for cancer-specific vaccines.
- Recognizing how certain bacteria are cancer-promoting versus cancer-inhibiting could potentially tailor specific treatment with probiotics and/or antibiotics to directly affect tumor progression.

19.1 Introduction

The human microbiota is a collection of microorganisms including bacteria, fungi, archae and viruses that inhabit and colonize the epithelial surfaces of our body [1]. The microbiome affects physiologic functions, including metabolic functions, inflammatory responses, and immunity [2]. The gut bacteriome is comprised of approximately 3×10^{13} bacterial cells, with the number of bacterial cells present in the human body being roughly equivalent to the number of human cells [3]. The bacterial cells mainly maintain a commensal relationship with the human host, however in times of intestinal ecologic change, these bacteria may become pathobionts, capable of expanding and acquiring pathogenic characteristics [4]. The microbiota and the eukaryotic host relationship has, also in many cases, evolved into a mutualistic one, in such that each organism benefits from the other and the two can be viewed as a "superorganism".

In contrast to the relative stability of our genome, the microbiome is capable of changing in response to colonization at birth (and type of birth), nutrition, treatment with antibiotics or probiotics, geography and age [5–7]. The composition of the microbiome continues to evolve after birth for the first few years until it transforms into the "adult form" [6]. Intestinal epithelial homeostasis is maintained by continuous cross talk between the microbiome, immune system, and mucosal barrier [8]. The capacity of the microbiota to affect the inflammatory response suggests a role in which it can modulate cancer development, progression and the response to chemotherapy.

Pancreatic ductal adenocarcinoma (PDAC) is the seventh-leading cause of cancer related deaths worldwide, with rates being even higher in developed countries [9]. One of the potential barriers to response to immunotherapy in PDAC is the paucity of infiltrating T cells in the microenvironment of the tumor, therefore making it an immunologically "cold tumor" and limiting the activity of immune checkpoint therapies [10]. Preclinical studies suggest that modulating the microbiome could be a strategy for improving response to immunotherapy.

19.2 Bacterial Commensalism in the Human Host

The human adult microbiota consists of approximately 12 phyla with *Firmicutes* and *Bacteroidetes* being the most dominant, followed by *Actinobacteria*, *Fusobacteria*, and others [11]. Humans and their microbiome have an intimate relationship which begins at birth, where vaginally delivered neonates become colonized with species that colonize the vaginal canal (*Lactobacillus*, *Prevotella* spp.) [12]. The gastrointestinal tract of neonates delivered by Cesarean section can become colonized with skin species (*Corynebacterium* and *Staphylococcus*) [13]. By 3 years of age, the microbiota evolve into an adult-like state. After this age, the microbial composition stays relatively stable with small fluctuations with normal physiologic influences, except that it can become strongly altered in disease states, dietary changes or with antibiotic treatment (Fig. 19.1).

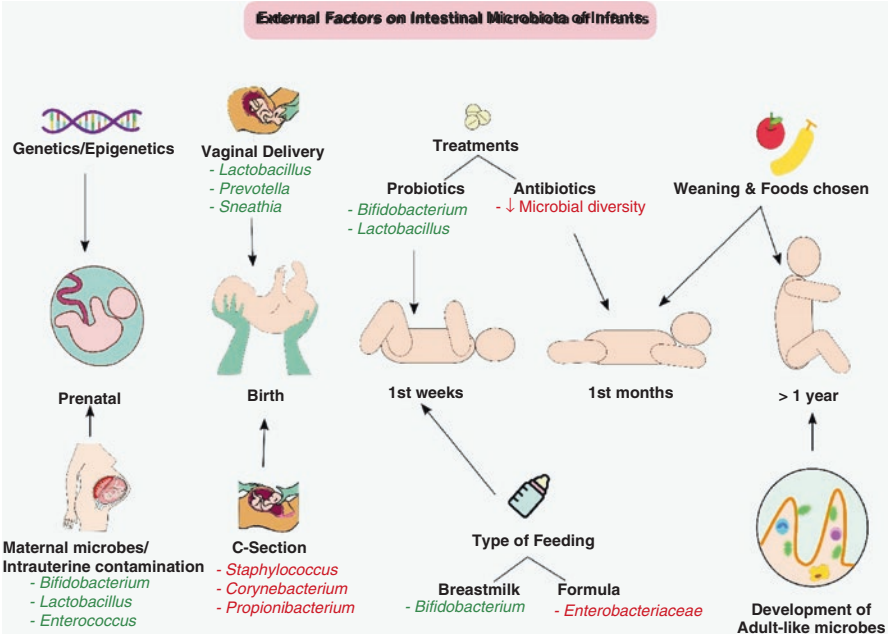

Fig. 19.1 Early influence on the microbiome. External factors affecting the intestinal microbiota of infants. Through infant developmental stages, multiple factors affect the constitution of intestinal microbiota. Beneficial modifications are highlighted in green and negative alterations are highlighted in red. At the prenatal stage, genetic factors or maternal microbes and intrauterine contamination can affect intestinal colonization. At birth, the delivery method is the main determining factor of gut microbiota. Type of feeding and probiotic/antibiotic treatments at weeks and months can contribute to alteration of intestinal microbes. Approximately at 1 year of age, infants accomplish adult-like gut microbe colonization. (Reprinted from [14]: *Early Disruption of the Microbiome Leading to Decreased Antioxidant Capacity and Epigenetic Changes: Implications for the Rise in Autism (Eshragi et al. Front. Cell. Neurosci., 15 August 2018)*)

19.3 Advances in Microbiome Research

Research aimed at elucidating the role the microbiome plays in our homeostasis as well in disease states has been severely limited until recently, due to improvements in technological capabilities. Culturing bacterial strains has always been the central principle to study of microbiology, however this classical approach has not been fruitful in the evaluation of the complexities of our gut microbiome, as most gut bacteria are unculturable or grow under tight anaerobic and nutritional conditions. Recent improvements in methodology (Fig. 19.2) allow for analysis using microbial

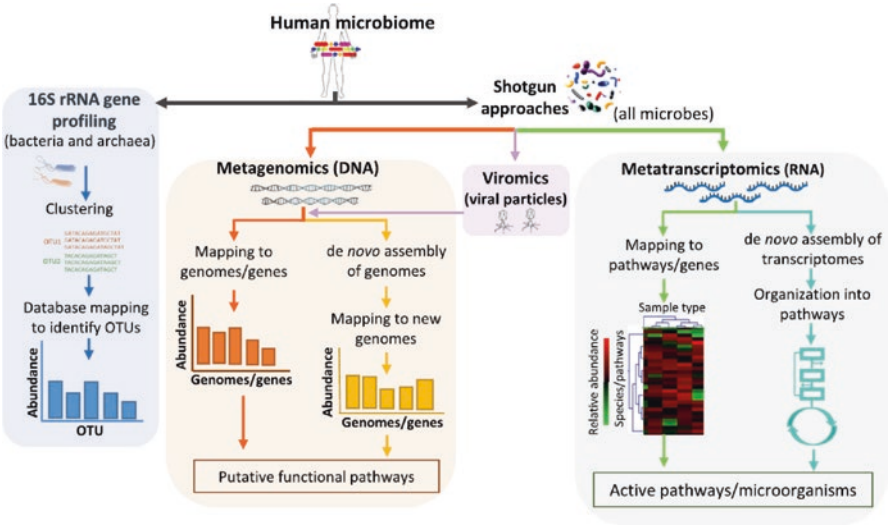

Fig. 19.2 Different sequencing and bioinformatic strategies for human microbiome analysis. In the 16S rRNA gene profiling the raw sequences obtained are passed through quality filters to minimize the presence of sequencing artifacts. The resulting filtered sequence reads are clustered into operational taxonomic units (OTUs), which represent similar organisms. After that, taxonomic identity is assigned for each OTU based in sequence homology against known 16S rRNA gene databases and the relative abundance of each OTU is calculated for each sample. The resulting OTUs table is also used for quantifying population diversity within and between the samples, as the alpha and beta diversity measurements, respectively. In the shotgun approaches, metagenomic, metatranscriptomic and viromic analyses are performed. In the metagenomic analysis, the DNA sequences obtained can either be mapped to reference genomes/genes or used for de novo assembly of genomes. Then the relative abundance of the present genomes/genes and the functional potential of the sequences can be assessed using functional annotated databases. In viromics analysis, first the viral particles (VPs) must be enriched and posteriorly sequenced to obtain the virus genomes. Furthermore, to analyze the active genes and species of the microbiome, the metatranscriptomic analysis is applied and the obtained RNA sequences are mapped to reference pathways and genes. The results are used to identify the active pathways, genes and microorganisms. Thus, the relative abundance of each active pathway/gene/microorganism in the human microbiome is determined. The de novo assembly of genomes and transcriptomes can be also performed to identify novel genomes or pathways. (Reprinted from [18]: *S. Bikel et al. Computational and Structural Biotechnology Journal 13 (2015) 390–401*)

sequencing with 16s ribosomal RNA (rRNA) and whole genome sequencing. This approach can allow the taxonomic characterization of species for further mechanistic studies. 16s rRNA sequencing is based on selective amplification of sequence part of the gene that encodes the 16s rRNA [15]. Because bacterial identification is based on a portion of the 16s rRNA gene, species level characterization of the bacteria is not achievable through this method, and is limited to the family or genus level [16]. Metagenomic shotgun sequencing can also be performed, which generates short reads representing the whole genomic content within an environmental sample [17]. Compared to 16s rRNA sequencing, shotgun sequencing allows for identification down to the species and strain level, therefore also allowing characterization of non-bacterial parts of the microbiota and also helps to do a functional characterization of the microbiome.

The use of germ-free mice has played a crucial role in evaluating the link between the microbiome in cancer and other diseases. This link becomes increasingly evident when conventionally raised specific pathogen-free mice are compared to germ free mice. Germ free mice are bred and maintained in environments to keep them lacking of detectable microbiota during their lifespan. Gnotobiotic mice have defined microbial compositions and include germ free mice as well as germ free mice that have been colonized with specific microbial communities.

19.3.1 Microbiota-Immune Cross-Talk

Recent studies have demonstrated a strong relationship between the microbiota and the host immune system, including both the adaptive and innate immune system. Microbial impact on the immune system was first described in studies performed in the 1950s and 1960s on germ free animals [19, 20]. Germ free mice studies have demonstrated the role the microbiome plays in local mucosal immunity, as these mice are more susceptible to infections. These deficiencies can be corrected by colonizing the gut with commensal bacteria. Germ free mice have less mucus-producing goblet cells, which are the first line of defense against pathogens in the intestine. Other immunodeficiencies in germ free mice include smaller Peyer's patches, decreased mesenteric lymph nodes, lack of lymphoid follicles in the lamina propria (LP), over-activation of anti-inflammatory T helper (Th) type 2 cytokines, and decreased expression of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) [21]. Remarkably, these changes disappear when the mice gut is colonized with microbiota from specific pathogen-free mice (conventionalization) [22, 23]. The phenomenon has also been described in studies comparing the immune systems of laboratory mice versus feral mice [24]. Laboratory specific pathogen-free mice, as neonatal humans, lack $CD8^+$ T cell differentiation, whereas these cell populations are present in feral and pet store mice. When the laboratory mice are cohoused with pet store mice, the immune system mature in the former. This transfer of microbiota also leads to an increase in resistance to the influenza virus [25].

Additional support for the microbial-based immune modification comes from research evaluating TLRs and adaptive immunity of the gut mucosa [26, 27]. The lamina propria of the gut is an abundant source of lymphocytes. A balanced interaction exists between the arms of the adaptive immune system (Tregs, Th1, Th2, Th17), which when disrupted can increase the propensity to develop certain autoimmune diseases, in particular colitis [28]. Bacteroides fragilis and Clostridia can induce $Foxp3^+$ Tregs [29, 30]. When Bacteroides fragilis colonizes the germ free mouse intestine, an increase in splenic Th1 polarized $CD4^+$ fraction is observed, which is also seen in specific pathogen-free mice. Genetically identical mice purchased from different laboratory vendors have been found to have different microbiota, leading to studies in which these mice were cohoused with each other, revealing that the Th17 cell phenotype from one breed could be transferred to the other. Analyzing the microbiome of these mice demonstrated that a segmented filamentous bacteria (Candidatus arthomitus) was responsible for the observed phenomenon [31, 32].

Epidemiological studies have also demonstrated the gut microbiota interact with the human immune system. As previously mentioned, neonates delivered via cesarean become colonized by skin commensals (*Staphylococcus*, *Corynebacterium*) rather than the normal flora of the adult vagina. The infants have higher incidences of developing autoimmune diseases later in life, such as diabetes, celiac disease, inflammatory bowel diseases, food allergies, and juvenile arthritis when compared to vaginally-delivered neonates [33–36]. Another protective factor in early infancy is the role that breast milk plays in establishing a core gut microbiome. Infants who are exclusively breastfed have a decreased risk of developing asthma later in life. Furthermore, breastmilk acts as a natural symbiotic, facilitating the colonization of protective *Bifidobacterium* in the neonatal intestine. Early and prolonged exposure to antibiotics creates a gut dysbiosis, increasing the risk of later development of inflammatory bowel disease, obesity, and cancer [37–40]. These studies demonstrate as a whole, the importance of the microbiome in the development of the innate and adaptive immune systems in mice and humans.

19.4 Microbiota and Cancer

Bacteria and viruses account for >15% of newly diagnosed human cancers globally, i.e. *Helicobacter pylori*, human papillomavirus, hepatitis B, hepatitis C, Epstein-Barr viruses [41]. However, the relationship between the microbiome and cancer remains understudied. Early studies demonstrated the link between the parasite *Schistosoma haematobium* and bladder cancers [42]. However, a firm link between microbial species and cancer was not established until Barry Marshall and Robin Warren discovered crucial evidence that the Gram-negative spiral bacterium *Campylobacter pylori* (later *Helicobacter pylori*) causes chronic gastritis and peptic ulcer disease [43, 44]. Peptic ulcers and severe gastritis, which are associated with an increased risk of gastric adenocarcinoma, were until then thought to be secondary to other external factors, such as stress, spicy foods, and lifestyle. This discovery led to the use of antibiotic treatment (as well as an *H. pylori* antigen-specific

vaccine) to eradicate *H. pylori* to prevent cancer [45, 46]. Treatment to eradicate *H. pylori*, in conjunction with other factors, can be attributed to for the decrease in gastric cancer incidence over the last century [47].

The link between cancer and bacteria has also been shown in colorectal cancer (CRC), where the gut microbiota directly interact with the site of tumorigenesis. Many epidemiologic studies have established the role of the "Western" diet, characterized by high consumption of red meat, animal fat, processed carbohydrates, and decreased fiber, in inducing intestinal dysbiosis [48–50]. Studies suggest that routine intake of this diet decrease microbial diversity and enriches *Firmicutes*, while decreases the colonization of *Prevotella*, *Xylanibacter* (*Bacteroidetes*), which decreases the *Bacteroidetes* to *Firmicutes* ratio and causes increased gut permeability [51, 52]. Additionally, dysbiosis secondary to prolonged use of antibiotics, has also been linked to an increased risk of development of colonic adenomas [40]. *Bacteroides fragilis and Fusobacterium nucleatum* promote CRC in pre-clinical mice models through promotion of immune cells into the tumor [53, 54].

19.5 Gut Microbiome Link to Cancer Immunotherapy Response

Multiple studies support that gut microbes can profoundly influence the action of immunotherapies. Pioneer work in understanding this link was done by injecting patients with heat-inactivated *Streptococcus* and *Serratia* species to stimulate the immune system, leading to sarcoma regression [55]. Similarly, Bacillus Calmette-Guerin has been used as a therapeutic agent for treatment of bladder cancer [56]. More recent work has examined the efficacy of immune checkpoint inhibitors in their role for treating cancer. Low doses of cyclophosphamide (an alkylating agent) can be used in conjunction with cancer vaccines, leading to induction of a Th1 phenotype and infiltration of Th17 cells into the tumor microenvironment [57]. It has also been discovered that microbes can induce Th17 cells, which in turn play a role in antimicrobial defense. These two phenomena were observed, and Viaud et al. suggested that the changes in the gut microbiome explain the immunotherapeutic activity of cyclophosphamide. Treatment with cyclophosphamide leads to intestinal dysbiosis-mediated increased gut permeability, which in turn causes translocation of Gram-positive bacteria to lymphoid tissue, causing activation of interferon (IFN)-gamma$^+$ Th17 (pathogenic Th17) cells [58].

Initial evidence of the role of specific microbes in modulating immune checkpoint inhibitors was performed in pre-clinical mouse models using CTLA-4 and PD-1/PD-L1 inhibitors. *B. fragilis* was found to enhance the efficacy of anti-CTLA-4 via a mechanism that involves activation of Th1 cells with cross-reactivity to bacterial antigens and tumor neoantigens. Administration of oral *Bifidobacterium* increased CD8$^+$ tumor-specific T cell mediated tumor infiltration and IFN-y production, as well as basal tumor control and anti-PD-L1 efficacy via activation of splenic and intratumoral dendritic cells [59]. These murine model studies established the importance of the microbiota in cancer immune checkpoint inhibitor therapy and

inspired the further pursuits to evaluate the microbiome's impact on anti-CTLA-4 and anti-PD-1/PD-L1 therapies in patients.

Studies from multiple institutions have described the link between the gut microbiota and immunotherapy efficacy in cancer patients [60–63]. DNA sequencing was performed on stool samples obtained from patients prior to initiation of immune checkpoint inhibitors, which identified an association between the gut microbial composition and therapeutic response. Specific bacterial taxa were overrepresented in patients labeled as "responders", whereas other distinct bacterial sequences were overrepresented in "non-responders". Interestingly, only certain bacteria were identified consistently across the multiple studies. This discrepancy between the bacterial populations may represent multiple factors, including patient geographic locations, genetic factors, as well as technical differences (such as fecal collection, DNA extraction and sequencing). To further examine the described phenomenon between responders versus non-responders, human microbiota "avatars" (germ free mice colonized with bacteria from patient-derived stools) have been used. Data from these studies recapitulates the results from human studies [60, 61]. Germ free mice who were reconstituted with responder patient commensals showed a greater response to immune checkpoint inhibitors than mice colonized with non-responder patient commensals.

Beyond just clinical response to therapy, immune-related toxicity of immune checkpoint inhibitors has also been associated with the gut microbiome composition. Based on stool analysis of samples obtained from patients treated with an anti-CTLA-4 antibody, bacteria from *Bacteroidetes phylum* were associated with lower rate of drug-induced colitis [64].

19.6 The Microbiome and Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is anticipated to become the second largest cause of cancer-related mortality in the United States. This, in part, is secondary to early metastatic spread to immunotolerant organs like the liver, leading to unresectable disease often found at initial diagnosis. Furthermore, the promising response that has been seen in various other cancers to immune checkpoint inhibitors has not been mirrored in treating PDAC, except in a few rare cases involving mismatch repair-deficiency.

19.6.1 Preclinical Studies in Pancreatic Cancer

Multiple studies have shown that pancreatic cancer is an inflammation-driven cancer. Inflammatory-driven changes from stimuli like cerulein-induced pancreatitis, obesity, lipopolysaccharide, and up-regulation of downstream inflammatory pathways like nuclear factor-kB, IL6-Stat 3, are essential to induce neoplasia in mice who harbor the oncogenic *Kras* mutation [65–68].

Immune cells and stroma and both essential parts of the tumor microenvironment (TME), which work together to sustain this inflammation-driven tumorigenesis. Kras induces infiltration of gdT cells, granulocyte macrophage colony-stimulating

factor-induced myeloid-derived suppressor cells, Th17 cells, Th2 cells, IL35^{+} Bregs, all which inhibit the infiltration of effector Th1 and Tc1 cell, thereby promoting tumorigenesis [69–73]. Additionally, PDAC stroma induces a pro-inflammatory environment via Th2, protecting the tumor from the anti-cancer response and keeping the tumor immunologically "cold" [74–76]. Conversely, induction of Th1 immunity increases survival in mice in humans, and also improves response of PDAC to immune checkpoint inhibitors [10]. This therefore suggests that immunotherapeutic agents may be effective treatment options if the TME components are properly targeted. Given this understanding, recent evidence has implicated the microbiome as important cancer-promoting components.

The role of the innate immune system, including PRRs and their ligands (microbe-associated molecular patterns) and their downstream targets has been studied in mouse models and been linked to the development of pancreatic disease (Fig. 19.3). We and others have reported that ligation of TLR 4, bacterial sensors, Nucleotide-binding oligomerization domain-containing protein 1 (NOD1), and NLRP3 inflammasome, increases the severity of acute pancreatitis in mice, and administration of oral antibiotics reverses this effect [77–79].

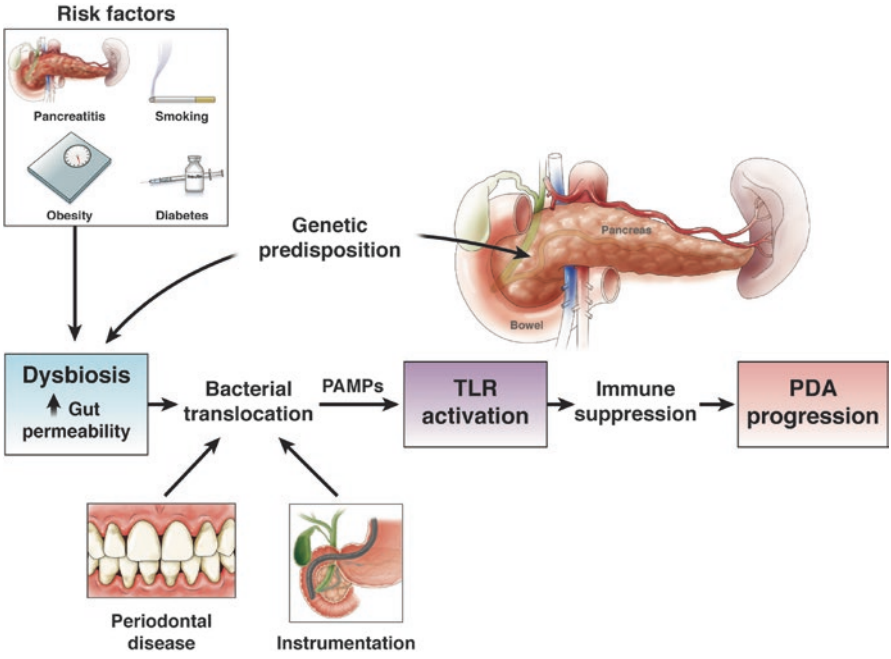

Fig. 19.3 Mechanism by which bacteria may access the pancreas and promote cancer. Inflammatory pathologies like pancreatitis and obesity are associated with increased gut permeability and dysbiosis, thereby, leading to possible bacterial translocation. Environmental insults like endoscopic retrograde cholangiopancreatography may also cause retrograde passage of bacteria from the duodenum through the pancreatic duct. In the pancreas, bacterial ligands pathogen-associated molecular pattern stimulate pattern recognition receptors (like TLRs) and cause downstream immune suppression, leading to development of PDA in the setting of heightened genetic risk. (Figure reprinted with permission from [80]: *The Role of the Microbiome in Immunologic Development and its Implication For Pancreatic Cancer Immunotherapy (Sethi et al.; Gastroenterology 2019;1–19)*)

Data from our laboratory suggested that PDAC-bearing $Kras^{G12D/+}$; $Trp53^{R172H/+}$; Pdx-1-Cre (KPC) have a very different gut microbiome when compared to control (Cre) mice [81]. We found that mouse pups that are "cohoused" with tumor-bearing KPC mice, the pups develop more aggressive pancreatic cancer xenografts, compared to pups that are cohoused with non-cancer bearing mice [82]. Furthermore, we found that eradication of the microbiome by routinely used broad spectrum antibiotics significantly decreases tumor burden in multiple murine models of PDAC (as well as melanoma and colon cancer) through an adaptive immune-dependent mechanism [83].

The microbiota promote the infiltration of pro-tumorigenic $IL17A^+$ $CD4^+$ $Th17^+$ cells while decreasing anti-tumor IFN-gamma$^+$ $CD4^+$ $Th1^+$ cells in the TME. Using a IL-17A-neutralizine monoclonal antibody abolishes the tumor-attenuating effects seen with antibiotic administration. 16s rRNA sequencing also suggests that PDAC metastatic lesions harbor a rich microbial environment, which interestingly, closely resembles the gut microbiome. Additionally, oral antibiotics also significantly decrease this metastatic-microbiome. Other studies have supported these findings, in both mice and humans, demonstrating that the tumor itself harbors a distinct microbiota, compared to cancer-naïve tissue. Germ free mice have significantly decreased tumor burden in multiple models of PDAC [84]. A comparison of the gut microbiomes of Ptf1aCre; LSL-KrasG12D and wild-type mice found that certain bacterial taxa are enriched at distinct time points in the development of PDAC, and taking feces from mice who have PDAC and performing a fecal transplant on Ptf1aCre; LSL-KrasG12D mice promotes and accelerates tumorigenesis. Interestingly, PDAC patients have a selective enrichment of *Proteobacteria*, *Synergistetes*, and *Euryarcheota* in their feces in comparison to healthy control patients.

Upon recognition of bacteria by TLR2 and TLR5, the gut microbiome induce a pro-tumoral immunosuppression within the tumor. By eradicating the microbiome with antibiotics, T cells polarize to a Th1 and Tc1 phenotype, and intratumoral macrophages polarize to an anti-tumor M1 phenotype. *Bifidobacterium pseudolongum* has been found to promote PDAC in a TLR-dependent manner. Antibiotics are able to up-regulate PD-1 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, leading to enhancement of response to aPD-1 immunotherapy.

Gemcitabine remains the major chemotherapy used in treatment of PDAC patients. However, tumors can become chemoresistant to the drug through various mechanisms, which contributes to decrease in overall survival of these patients. Geller et al. found that bacterial metabolism may play in important role in the development of resistance to gemcitabine [85]. *Mycoplasma hyorhinis* and *Gammaproteobacteria* can metabolize gemcitabine into inactive compounds through deamination, leading to its chemoresistance. Inhibiting the enzyme involved in this deamination or by treating with antibiotics, such as ciprofloxacin, increases response to gemcitabine. Furthermore, *Gammaproteobacteria* are found in pancreatic tumors of patients who undergo surgery (causes manipulation of the pancreatic duct) [86].

Evaluation of the mycobiome in PDAC has also revealed that the intrapancreatic fungal population within pancreatic tumors, is different when compared to the gut mycobiome as well as normal, healthy pancreatic tissue [87]. This phenomenon was also observed in human PDAC patients, with *Malassezia* more prevalent in tumor tissue than in the gut. In murine studies performed by Aykut et al., treatment with fluconazole was protective against tumor progression.

19.7 Clinical Studies

Multiple studies performed over the recent years have demonstrated the link between oral, gut and intratumoral bacteria in pancreatic cancer (Table 19.1). Several bacteria have been found to be enriched in the gastrointestinal tract of

Table 19.1 Epidemiological studies investigating the microbiome in pancreatic cancer patients

Microbe(s)/risk factor studied	Study design	No. of patients	Key findings	Reference
Helicobacter pylori (CagA±) through serology	Meta-analysis	6 studies (822 pancreatic cancer [PC] patients, 1513 controls)	Weak association (OR, 1.38; 95% CI, 1.08–1.75)	[94]
	Meta-analysis	9 studies (1083 PC patients, 1950 controls)	Weak association (OR, 1.47; 95% CI, 1.22–1.77)	[95]
	Meta-analysis	5 studies (1446 PC patients, 2235 controls)	No association (OR, 0.99; 95% CI, 0.65–1.50)	[96]
Self-reported history of periodontitis	Questionnaire-based prospective	48,375 males (216 PC patients)	Periodontitis was a risk factor for PC development (RR, 1.64; 95% CI, 1.19–2.26)	[89]
Oral microbiome (microarray and qPCR)	Case–control	10 PC patients and 10 controls (candidates validated with 28 PC patient and 28 controls)	PC patients had different salivary flora as compared to controls. Neisseria elongata and Streptococcus mitis were increased in PC patients (ROC AUC for both, 0.9; 95% CI, 0.78–0.96)	[97]
Oral microbiome (plasma antibodies)	Nested case–control	405 PC patients and 416 controls	Significant association of PC with increased antibodies against Porphyromonas gingivalis (OR, 2.14; 95% CI, 1.05–4.36)	[88]
Oral microbiome (16s rRNA gene sequencing)	Nested case–control	361 PC patients and 371 controls	P. gingivalis and Aggregatibacter actinomycetemcomitans were significantly associated with PC (OR for presence vs. absence, 1.60 and 2.20; 95% CI, 1.15–2.22 and 1.16–4.18, for P. gingivalis and A. actinomycetemcomitans respectively)	[90]

(continued)

Table 19.1 (continued)

Microbe(s)/risk factor studied	Study design	No. of patients	Key findings	Reference
Intratumoral Fusobacterium (PCR array)	Cases only	283 PC patients	8.8% samples tested positive for Fusobacterium and out of those, 28% had Fusobacterium in noncancerous pancreas	[98]
Intratumoral bacteria (qPCR and 16s rRNA gene sequencing)	Case–control	113 PC patients and 20 controls	PC samples had increased presence of bacterial DNA in PDAC samples as compared to controls (76% vs. 15%; $P < 0.005$)	[85]
	Cases only	65 PC patients	Gammaproteobacteria were the most abundant intratumoral bacteria	
Intratumoral bacteria (qPCR and 16S rRNA gene sequencing)	Case–control	12 PC patients and 5 controls	PC patients had increased bacterial DNA load as compared to controls. Proteobacteria, Bacteroidetes, Firmicutes, Pseudomonas and Elizabethkingia were found abundantly in PC tissue	[84]
Fecal bacteria (16S rRNA gene sequencing)	Case–control	32 PC patients and 31 controls	Increased abundance of Proteobacteria, Synergistetes, Euryarchaeota differentiated PC patients from controls	
Intratumoral bacteria (qPCR and 16s rRNA gene sequencing)	Cohort	Cohort 1: 22 Long Term Survivors (LTS) and 21 Short Term Survivors (STS) Cohort 2: 15 Very Long Term Survivors and 10 STS	LTS had increased alpha diversity compared to STS in both cohorts. LTS had predominance of Alphaproteobacteria, Sphingobacteria, and Flavobacteria compared to STS (dominated by Clostridia and Bacteroidea)	[93]
Intratumoral fungi and fecal fungi (qPCR and 18s rRNA sequencing)	Case-control	3 PC patients and 3 Controls; Gut (18) and tumour (13) biologically independent specimens, patients with PC	Malassezia more abundant in tumor tissue than in gut. There were distinct clusters of fungal communities in the tumour tissue and gut of patients with PC	[87]

Reprinted and modified with permission from [80]: *The Role of the Microbiome in Immunologic Development and its Implication For Pancreatic Cancer Immunotherapy (Sethi et al; Gastroenterology 2019;1–19)*

AUC area under the curve, *CI* confidence interval, *OR* odds ratio, *qPCR* quantitative polymerase chain reaction, *ROC* receiver operating characteristic, *RR* relative risk, *rRNA* ribosomal RNA

PDAC patients. Periodontitis and oral dysbiosis, which is characterized by overcolonization of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are risk factors for development of PDAC [85, 88–90]. Oral bacteria that disseminate systemically and can cause bacterial endocarditis, may also lead to biofilm formation in the pancreatic duct [91]. Therefore, it is possible that these bacteria can translocate from the duct to the pancreas, promoting the formation of PDAC.

Bacteria can also potentially migrate to the duodenum, as patients diagnosed with PDAC who undergo endoscopic retrograde cholangiopancreatography (ERCP) have increased intratumoral bacterial burden compared to those without ERCP performed [85].

Bacterial transmission to the pancreas can also occur through a paracellular route in the setting of increased gut permeability, which is seen in pancreatitis and obesity, both of which are significant risk factors for the development of PDAC [92].

Diversity within the microbiome can be described by richness and evenness. Alpha-diversity refers to number of species relative to the species abundance within a sample. Beta diversity refers to the diversity between samples. A higher alpha diversity within the gut microbiome has been linked to a "healthy" state [11]. Riquelme et al. analyzed the tumor microbiome diversity in PDAC patients via 16s sequencing, revealing greater alpha-diversity was present in patients that were long-term survivors versus short-term survivors. Furthermore, a signature intra-tumoral microbiome (Fig. 19.4) was associated with long-term survival [93].

19.8 Conclusion

There have been many advances offering insight into the complex role the microbiota plays in modulating cancer progression through cross-talk with the immune system. More research is needed to fully decipher the intricacies of this relationship. It has become evident that certain bacteria form a beneficial commensal relationship with the human host, whereas other bacteria can have unfavorable effects. In this context, it is possible that the future of cancer therapeutics may involve targeting these "bad" bacteria to halt tumor progression.

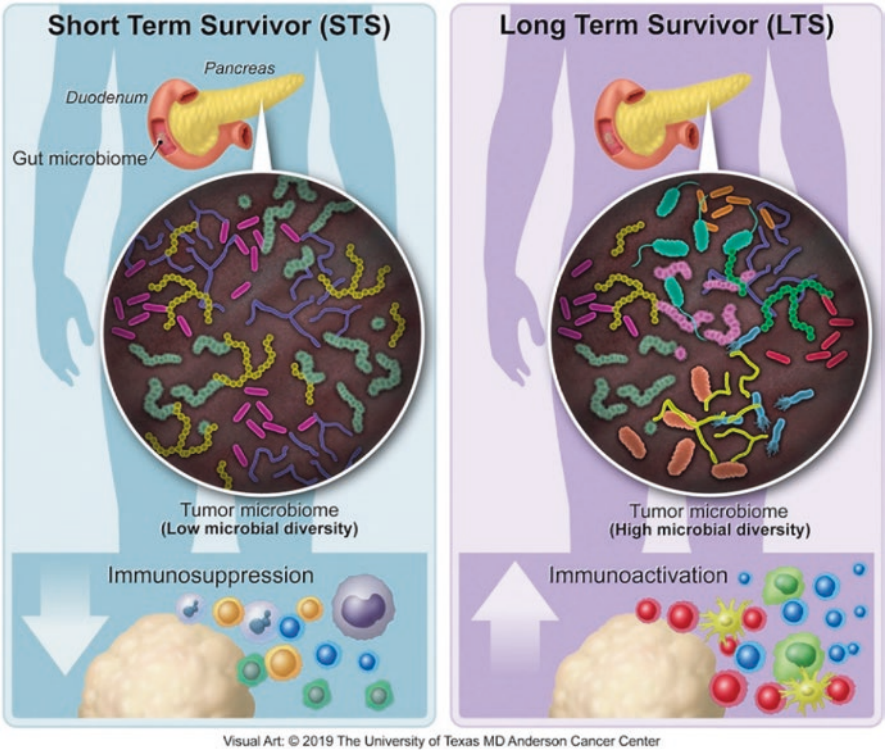

Fig. 19.4 Survival differences depending on microbiome in pancreatic tumours. (Figure reprinted with permission from [93]: *Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes (Riquelme et al.; Cell Volume 178, Issue 4, 8 August 2019, Pages 795–806.e12)*)

References

1. Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The application of ecological theory toward an understanding of the human microbiome. Science. 2012;336(6086):1255–62.
2. Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L, Trinchieri G. The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. Eur J Immunol. 2015;45(1):17–31.
3. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533.
4. Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. Curr Opin Immunol. 2011;23(4):473–80.
5. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486(7402):222–7.
6. Backhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17(5):690–703.
7. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971–5.

8. Wells JM, Rossi O, Meijerink M, van Baarlen P. Epithelial crosstalk at the microbiota-mucosal interface. Proc Natl Acad Sci U S A. 2011;108(Suppl 1):4607–14.
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
10. Winograd R, Byrne KT, Evans RA, Odorizzi PM, Meyer AR, Bajor DL, et al. Induction of T-cell immunity overcomes complete resistance to PD-1 and CTLA-4 blockade and improves survival in pancreatic carcinoma. Cancer Immunol Res. 2015;3(4):399–411.
11. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207–14.
12. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends Mol Med. 2015;21(2):109–17.
13. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. J Nutr. 2008;138(9):1796S–800S.
14. Eshraghi RS, Deth RC, Mittal R, Aranke M, Kay SS, Moshiree B, et al. Early disruption of the microbiome leading to decreased antioxidant capacity and epigenetic changes: implications for the rise in autism. Front Cell Neurosci. 2018;12:256.
15. Nguyen NP, Warnow T, Pop M, White B. A perspective on 16S rRNA operational taxonomic unit clustering using sequence similarity. NPJ Biofilms Microbiomes. 2016;2:16004.
16. Ma J, Prince A, Aagaard KM. Use of whole genome shotgun metagenomics: a practical guide for the microbiome-minded physician scientist. Semin Reprod Med. 2014;32(1):5–13.
17. Prakash T, Taylor TD. Functional assignment of metagenomic data: challenges and applications. Brief Bioinform. 2012;13(6):711–27.
18. Bikel S, Valdez-Lara A, Cornejo-Granados F, Rico K, Canizales-Quinteros S, Soberon X, et al. Combining metagenomics, metatranscriptomics and viromics to explore novel microbial interactions: towards a systems-level understanding of human microbiome. Comput Struct Biotechnol J. 2015;13:390–401.
19. Thorbecke GJ, Benacerraf B. Some histological and functional aspects of lymphoid tissue in germfree animals. II. Studies on phagocytosis in vivo. Ann N Y Acad Sci. 1959;78:247–53.
20. Gordon HA, Wostmann BS. Morphological studies on the germfree albino rat. Anat Rec. 1960;137:65–70.
21. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009;9(5):313–23.
22. Schaedler RW, Dubs R, Costello R. Association of germfree mice with bacteria isolated from normal mice. J Exp Med. 1965;122:77–82.
23. Dewhirst FE, Chien CC, Paster BJ, Ericson RL, Orcutt RP, Schauer DB, et al. Phylogeny of the defined murine microbiota: altered Schaedler flora. Appl Environ Microbiol. 1999;65(8):3287–92.
24. Beura LK, Hamilton SE, Bi K, Schenkel JM, Odumade OA, Casey KA, et al. Normalizing the environment recapitulates adult human immune traits in laboratory mice. Nature. 2016;532(7600):512–6.
25. Rosshart SP, Vassallo BG, Angeletti D, Hutchinson DS, Morgan AP, Takeda K, et al. Wild mouse gut microbiota promotes host fitness and improves disease resistance. Cell. 2017;171(5):1015–28. e13
26. Re F, Strominger JL. Toll-like receptor 2 (TLR2) and TLR4 differentially activate human dendritic cells. J Biol Chem. 2001;276(40):37692–9.
27. Abrahams VM, Bole-Aldo P, Kim YM, Straszewski-Chavez SL, Chaiworapongsa T, Romero R, et al. Divergent trophoblast responses to bacterial products mediated by TLRs. J Immunol. 2004;173(7):4286–96.
28. Omenetti S, Pizarro TT. The Treg/Th17 Axis: a dynamic balance regulated by the gut microbiome. Front Immunol. 2015;6:639.
29. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, de Roos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451–5.

30. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;504(7480):446–50.
31. Ivanov II, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe. 2008;4(4):337–49.
32. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009;139(3):485–98.
33. Tollanes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population-based cohort study. J Pediatr. 2008;153(1):112–6.
34. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? J Allergy Clin Immunol. 2003;112(2):420–6.
35. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51(5):726–35.
36. Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. Pediatrics. 2015;135(1):e92–8.
37. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol. 2008;6(11):e280.
38. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol. 2010;105(12):2687–92.
39. Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. Int J Obes. 2013;37(1):16–23.
40. Cao Y, Wu K, Mehta R, Drew DA, Song M, Lochhead P, et al. Long-term use of antibiotics and risk of colorectal adenoma. Gut. 2018;67(4):672–8.
41. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016;4(9):e609–16.
42. Mustacchi P, Shimkin MB. Cancer of the bladder and infestation with Schistosoma hematobium. J Natl Cancer Inst. 1958;20(4):825–42.
43. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311–5.
44. Marshall BJ, Armstrong JA, McGechie DB, Glancy RJ. Attempt to fulfil Koch's postulates for pyloric Campylobacter. Med J Aust. 1985;142(8):436–9.
45. Vakil N, Megraud F. Eradication therapy for Helicobacter pylori. Gastroenterology. 2007;133(3):985–1001.
46. Zeng M, Mao XH, Li JX, Tong WD, Wang B, Zhang YJ, et al. Efficacy, safety, and immunogenicity of an oral recombinant Helicobacter pylori vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386(10002):1457–64.
47. Balakrishnan M, George R, Sharma A, Graham DY. Changing trends in stomach cancer throughout the world. Curr Gastroenterol Rep. 2017;19(8):36.
48. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA. 2007;298(7):754–64.
49. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin N Am. 2002;31(4):925–43.
50. Burkitt DP. Epidemiology of large bowel disease: the role of fibre. Proc Nutr Soc. 1973;32(3):145–9.
51. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010;107(33):14691–6.
52. Serino M, Luche E, Gres S, Baylac A, Berge M, Cenac C, et al. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut. 2012;61(4):543–53.
53. Wu S, Rhee K-J, Albesiano E, Rabizadeh S, Wu X, Yen H-R, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009;15(9):1016–22.

54. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe. 2013;14(2):207–15.
55. Coley WB. II. Contribution to the knowledge of sarcoma. Ann Surg. 1891;14(3):199–220.
56. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116(2):180–3.
57. Viaud S, Flament C, Zoubir M, Pautier P, LeCesne A, Ribrag V, et al. Cyclophosphamide induces differentiation of Th17 cells in cancer patients. Cancer Res. 2011;71(3):661–5.
58. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science. 2013;342(6161):971–6.
59. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 2015;21(37):10609–20.
60. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91–7.
61. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97–103.
62. Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, et al. Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia. 2017;19(10):848–55.
63. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol. 2017;28(6):1368–79.
64. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016;7:10391.
65. Guerra C, Schuhmacher AJ, Canamero M, Grippo PJ, Verdaguer L, Perez-Gallego L, et al. Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell. 2007;11(3):291–302.
66. Daniluk J, Liu Y, Deng D, Chu J, Huang H, Gaiser S, et al. An NF-kappaB pathway-mediated positive feedback loop amplifies Ras activity to pathological levels in mice. J Clin Invest. 2012;122(4):1519–28.
67. Chang HH, Moro A, Takakura K, Su HY, Mo A, Nakanishi M, et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in KrasG12D mice. PLoS One. 2017;12(9):e0184455.
68. Ling J, Kang Y, Zhao R, Xia Q, Lee DF, Chang Z, et al. KrasG12D-induced IKK2/beta/NF-kappaB activation by IL-1alpha and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(1):105–20.
69. Daley D, Zambirinis CP, Seifert L, Akkad N, Mohan N, Werba G, et al. gammadelta T cells support pancreatic oncogenesis by restraining alphabeta T cell activation. Cell. 2016;166(6):1485–99.e15.
70. Pylayeva-Gupta Y, Lee KE, Hajdu CH, Miller G, Bar-Sagi D. Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. Cancer Cell. 2012;21(6):836–47.
71. McAllister F, Bailey JM, Alsina J, Nirschl CJ, Sharma R, Fan H, et al. Oncogenic Kras activates a hematopoietic-to-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. Cancer Cell. 2014;25(5):621–37.
72. Ochi A, Nguyen AH, Bedrosian AS, Mushlin HM, Zarbakhsh S, Barilla R, et al. MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med. 2012;209(9):1671–87.
73. Mirlekar B, Michaud D, Searcy R, Greene K, Pylayeva-Gupta Y. IL35 hinders endogenous antitumor T-cell immunity and responsiveness to immunotherapy in pancreatic cancer. Cancer Immunol Res. 2018;6(9):1014–24.

74. Erez N, Truitt M, Olson P, Arron ST, Hanahan D. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-kappaB-dependent manner. Cancer Cell. 2010;17(2):135–47.
75. De Monte L, Reni M, Tassi E, Clavenna D, Papa I, Recalde H, et al. Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. J Exp Med. 2011;208(3):469–78.
76. Garg B, Giri B, Modi S, Sethi V, Castro I, Umland O, et al. NFkappaB in pancreatic stellate cells reduces infiltration of tumors by cytotoxic T cells and killing of cancer cells, via upregulation of CXCL12. Gastroenterology. 2018;155(3):880–91.e8.
77. Sharif R, Dawra R, Wasiluk K, Phillips P, Dudeja V, Kurt-Jones E, et al. Impact of toll-like receptor 4 on the severity of acute pancreatitis and pancreatitis-associated lung injury in mice. Gut. 2009;58(6):813–9.
78. Tsuji Y, Watanabe T, Kudo M, Arai H, Strober W, Chiba T. Sensing of commensal organisms by the intracellular sensor NOD1 mediates experimental pancreatitis. Immunity. 2012;37(2):326–38.
79. Hoque R, Sohail M, Malik A, Sarwar S, Luo Y, Shah A, et al. TLR9 and the NLRP3 inflammasome link acinar cell death with inflammation in acute pancreatitis. Gastroenterology. 2011;141(1):358–69.
80. Sethi V, Vitiello GA, Saxena D, Miller G, Dudeja V. The role of the microbiome in immunologic development and its implication for pancreatic cancer immunotherapy. Gastroenterology. 2019;156(7):2097–115.e2.
81. Hingorani SR, Wang L, Multani AS, Combs C, Deramaudt TB, Hruban RH, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell. 2005;7(5):469–83.
82. Sethi V, Kurtom S, Tarique M. Depletion of the gut microbiota decreases pancreatic cancer burden by modulating the immune system. Pancreatology. 2018;18:S90–1.
83. Sethi V, Kurtom S, Tarique M, Lavania S, Malchiodi Z, Hellmund L, et al. Gut microbiota promotes tumor growth in mice by modulating immune response. Gastroenterology. 2018;155(1):33–7.e6.
84. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov. 2018;8(4):403–16.
85. Geller LT, Barzily-Rokni M, Danino T, Jonas OH, Shental N, Nejman D, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. Science. 2017;357(6356):1156–60.
86. Olarerin-George AO, Hogenesch JB. Assessing the prevalence of mycoplasma contamination in cell culture via a survey of NCBI's RNA-seq archive. Nucleic Acids Res. 2015;43(5):2535–42.
87. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. Nature. 2019;574(7777):264–7.
88. Michaud DS, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjonneland A, et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut. 2013;62(12):1764–70.
89. Michaud DS, Joshipura K, Giovannucci E, Fuchs CS. A prospective study of periodontal disease and pancreatic cancer in US male health professionals. J Natl Cancer Inst. 2007;99(2):171–5.
90. Fan X, Alekseyenko AV, Wu J, Peters BA, Jacobs EJ, Gapstur SM, et al. Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut. 2018;67(1):120–7.
91. Swidsinski A, Schlien P, Pernthaler A, Gottschalk U, Barlehner E, Decker G, et al. Bacterial biofilm within diseased pancreatic and biliary tracts. Gut. 2005;54(3):388–95.
92. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, et al. Intestinal permeability—a new target for disease prevention and therapy. BMC Gastroenterol. 2014;14:189.
93. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell. 2019;178(4):795–806.e12.

94. Trikudanathan G, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. JOP. 2011 Jan 5;12(1):26–31. PMID: 21206097.
95. Xiao M, Wang Y, Gao Y. Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. PLoS One. 2013 Sep 26;8(9):e75559. doi: 10.1371/journal.pone.0075559. PMID: 24086571; PMCID: PMC3784458.
96. Chen XZ, Wang R, Chen HN, Hu JK. Cytotoxin-Associated Gene A-Negative Strains of Helicobacter pylori as a Potential Risk Factor of Pancreatic Cancer: A Meta-Analysis Based on Nested Case-Control Studies. Pancreas. 2015 Nov;44(8):1340–4. doi: 10.1097/MPA.0000000000000414. PMID: 26390415.
97. Farrell JJ, Zhang L, Zhou H, Chia D, Elashoff D, Akin D, Paster BJ, Joshipura K, Wong DT. Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. Gut. 2012 Apr;61(4):582–8. doi: 10.1136/gutjnl-2011-300784. Epub 2011 Oct 12. PMID: 21994333; PMCID: PMC3705763.
98. Mitsuhashi K, Nosho K, Sukawa Y, Matsunaga Y, Ito M, Kurihara H, Kanno S, Igarashi H, Naito T, Adachi Y, Tachibana M, Tanuma T, Maguchi H, Shinohara T, Hasegawa T, Imamura M, Kimura Y, Hirata K, Maruyama R, Suzuki H, Imai K, Yamamoto H, Shinomura Y. Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis. Oncotarget. 2015 Mar 30;6(9):7209–20. doi: 10.18632/oncotarget.3109. PMID: 25797243; PMCID: PMC4466679.

Chapter 20
Immuno-Oncology in Pancreatic Cancer

Nigel B. Jamieson and Colin W. Steele

Take Home Messages

- The tumour microenvironment of pancreatic cancer is an intricate network of signals between immune cells, cancer cells, and stroma, creating an immunosuppressive environment.
- The immune landscape is dominated by immunosuppressive cell types (tumour-associated macrophages, MDSC, and Treg cells) with a paucity of effector T cells.
- Attempts at single agent immuno-oncology therapies have had limited impact on pancreatic cancer, compared to other cancers types.
- Barriers associated with pancreatic cancer include upregulation of immunosuppressive pathway, lack of T-cell infiltrate and low mutational burden rates.
- Strategies to improve success include combinatorial approaches guided by in-depth microenvironmental assessment.

Pearls and Pitfalls

- Single agent immunotherapy trials have failed to impact upon disease in pancreatic cancer.
- Combinatorial trial strategies are in their infancy and will require stratified trial designs to incorporate those patients most likely to benefit.

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Future Perspectives

- To develop strategies to (1) increase initial T-cell priming, (2) overcome an immunosuppressive microenvironment, and (3) manage compensatory mechanisms of T-cell anergy and exhaustion.
- To develop mechanism-driven biomarkers to guide immune checkpoint blockade in pancreatic cancer therapy.
- Focus is required to trial immuno-oncology strategies in the localised disease setting in an effort to prevent metastasis.
- Explore the interaction between the microbiome, the immune landscape and response to therapy.

20.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) has overtaken breast cancer as the third most common cause of cancer related death in Western societies, and is predicted to be second by 2025 [1]. Tremendous scientific progress has been made over the past decade in understanding how to manipulate the immune system, translating into unprecedented, improved outcomes for certain stubborn, recalcitrant malignancies. However, for PDAC the impact of immunotherapy has been disappointing. Responses to immunotherapy in PDAC are vanishingly rare. Accumulating evidence from murine models and humans suggests the refractory nature is linked to the complex dichotomy that exists with the immune system simultaneously restraining and promoting PDAC [2].

While epidemiological level analysis suggests a correlation between chronic pancreatitis and PDAC, underlying mechanisms linking chronic inflammation in the pancreas to initiation and progression of PDAC are derived primarily from the study of murine models [3]. Pancreatitis is acknowledged as a critical initiator of PDAC in GEMMs which conditionally express mutant *Kras* in the pancreas from birth [4, 5]. Study of initiation models of PDAC have shown that multiple components of inflammation including IL-6, regulatory B-cells and innate immune cells including neutrophils and myeloid derived suppressor cells, can promote tumourigenesis in the context of mutant *Kras* [6].

In this chapter, we focus on the rationale supporting pursuit of an immuno-oncology strategy in PDAC, discuss the barriers limiting efficacy of immuno-therapeutics, and summarize preclinical and clinical strategies to sensitize PDAC to immunotherapy.

20.2 Impediment to Immunotherapy in PDAC

Despite rationale for targeting inflammatory pathways in PDAC, there has been little benefit observed at this point. Within the field, multiple obstacles have been shown to impede delivery, or effectiveness of immune oncological drugs in

pre-clinical models. These factors will be discussed below and investigators are working on tackling resistance mechanisms through multitargeted approaches to improve outcomes for patients.

20.2.1 Stroma

Despite the integral role played by inflammatory and immune pathways in PDAC development, clinical trials using single-agent immune checkpoint blockade have been unsuccessful thus far. The PDAC tumour microenvironment (TME), an abundance of non-cancer cell components, termed the stroma, represents a barrier to immunotherapy in both murine models and humans. Accounting for up to 50% of tumour volume, the dense hypovascular, fibrotic stroma can inhibit spontaneous and therapeutically induced anti-tumour immunity [7]. Desmoplastic stroma is thought to block the penetration of systemic therapies whilst simultaneously facilitating immune escape. Initial studies demonstrated that tumour incidence and metastasis increased when an increased proportion of pancreatic stellate cells were co-injected with PDAC cells, identifying the stroma as a potential target for therapeutic intervention [8]. Yet, in preclinical PDAC models, fibroblast depletion led to increased regulatory T-cells (Treg) accumulation and reduced survival, supporting a more intricate relationship between stroma and epithelial components [9]. This complexity likely explains the failure of the inhibition of Hedgehog signalling in clinical trials despite the apparent utility in preclinical models [10, 11]. Multiple novel strategies to overcome the stomal fibrosis integrity and facilitate T-cell activation are accumulating [7], and include inhibition of focal adhesion kinase-1 (FAK1) which improves chemotherapy and immunotherapy response in preclinical models [12]. Inhibition of lysyl oxidase (LOX), an enzyme necessary for collagen generation and cross-linking, in GEMM through a blocking antibody combined with gemcitabine reduced ECM cross-linking, blocked metastasis, and increased survival times compared to gemcitabine alone [13]. Targeting hyaluronic acid has been shown to improve vascular penetrance and survival in preclinical models [14] however, unfortunately in a recent phase 3 trial failed to outperform standard of care chemotherapy for patients with metastatic PDAC (NCT02715804). Yet a potential novel target for stromal manipulation, HSPG2 (perlecan), showed benefit when inhibition was combined with gemcitabine plus nab-paclitaxel [15].

20.2.2 T-Cells

The development of immune-based therapies for PDAC is challenging because of poor tumour antigenicity, and an immunosuppressive environment that promotes tumour escape through cellular and molecular suppressive components and leads to paucity of T-cell infiltration. Despite a relative paucity of T-cell infiltration which

results in the classical description of PDAC as a 'cold tumour,' significant variation of T-cell infiltration patterns exist in both murine [16] and human PDACs [17]. Ultimately, the correlation of $CD8^+$ T-cell density and outcome has encouraged the pursuit of immunotherapeutic strategies in PDAC. Most have T-cell populations skewed toward suppressive $CD4^+$ T-cell lineages, with $Foxp3^+$ Tregs recruited early, accounting for 25% of all $CD4^+$ T-cells in both pancreatic intraepithelial neoplasia (PanIN) and PDAC [18]. Reduced numbers of intratumoural Tregs [19] are associated with increased disease-free survival after pancreatectomy, suggesting that accumulation is an important determinant of survival in patients with PDAC. However, Treg depletion alone of has been insufficient to restore $CD8^+$ recruitment.

Recently, other pro-tumourigenic T-cell lineages have been described, with the γδ T-cells capable of inhibiting $CD3^+$ αβ T-cells through secreted and ligand-dependent mechanisms [20]. While Th17 cells have been shown to promote PDAC progression in an IL17-dependent manner [21]. Overall, PDAC generates a TME augmented by suppressive T-cell populations with a paucity of effector T-cells.

20.2.3 Immune Checkpoints

Multiple immune signalling pathways regulate anti-tumour immunity, involving costimulatory and inhibitory receptors (immune checkpoints) present on T-cells. Most studies of immunomodulatory agents in PDAC have examined the role of the inhibitory costimulatory receptors cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein-1 (PD-1). Both are critical for activation and suppressive activity of Tregs with a primary role of preventing excessive response to infection. Tumours utilise these pathways to induce Treg suppression, and therefore PDAC treatment must overcome immunosuppression in addition to immune activation for a durable response. Consistent with this, CTLA-4 and PD1-pathway expression are upregulated in PDAC [22], and both are correlated with reduced survival [23].

To date for patients with PDAC, immunotherapy has rarely yielded significant clinical impact [24]. Initial clinical trials investigating the targeting of PD-1/PDL1 did not reproduce the remarkable efficacy observed in metastatic melanoma and non-small cell lung cancer (NSCLC) [25, 26]. Other single agent immuno-oncology strategies have failed including CTLA-4 antagonists [27].

20.2.4 Myeloid Cells

A widespread strategy of immune escape employed by cancer is induction of altered myelopoiesis via secretion of metabolites, cytokines, and chemokines. Thus, promoting suppressive myeloid cells to accumulate in the TME capable of inhibiting

the anti-tumour T-cell response [28]. Broadly classified these cells are myeloid-derived suppressor cells (MDSCs; $CD11b^+CD33^+$—humans) and tumour-associated macrophages (TAMs; HLA-DR^+ $CD68^+$—humans). In murine models both MDSCs and TAMs have demonstrated the ability to induce T-cell suppression through secreted factors and by PDL1 induction [22]. Furthermore, depletion of macrophages outside of tumours has been illustrated to promote T-cell infiltration suggesting their role extends far beyond the TME [29].

In patients with PDAC, mobilisation of bone marrow derived monocytes is increased, with both $CD66b^+$ MDSCs and $CD68^+$ TAMs tumour infiltration associated with negative outcomes following resection [30]. Myeloid depletion appears to sensitise tumours to systemic therapies including chemotherapy, radiotherapy, and checkpoint blockade in murine models, supporting MDSCs as key negative regulators of immune reactivity in PDAC.

20.2.5 B-Cells

A more recently investigated suppressive component of the TME, B-cell recruitment is dependent on Bruton's Tyrosine kinase (BTK) [31], and CXCL13 [32] with evidence that B-cells promote PDAC tumourigenesis in murine models however the clinical significance requires clarification.

20.3 Current Immunotherapeutic Approaches

Approaches including specific inhibitors (antibodies and small molecule inhibitors) or a variety of signalling pathways are described. Other targeted immunotherapy strategies, e.g., oncolytic viruses, vaccines, and chimeric antigen receptor-T cell (CAR-T) therapies aim to target PDAC in a more focused manner while minimising side-effects. Furthermore, combining mainstay, untargeted therapeutic strategies, chemotherapy and radiotherapy with immune-checkpoint blockade is appropriate.

20.3.1 Combining Immune Checkpoint Inhibitors with Untargeted Therapies

20.3.1.1 Chemotherapy

While most immune therapies are being developed for use after patients have received chemotherapy, we have little, if any understanding of the molecular pathology of "post-chemotherapy" tumours [33], in PDAC. Given the complexity of the anti-tumour immune response, and the apparent failure of single agent strategies,

this has prompted the concept of combinatorial strategies with chemotherapy which have potential to alter the immune system [34, 35] and the TME [13, 36], with response to immune therapy potentially determined by the type of prior treatment [37]. Gemcitabine-based chemotherapy has often used as a backbone in these combination immunotherapy trials, as there is evidence of an increased tumour antigen availability, coinciding with transiently depleted immunosuppressive Tregs and MDSCs in the TME [35, 38, 39]. A selection of current immunotherapy combinatorial strategies are illustrated in Table 20.1.

Table 20.1 Select studies focusing on immune checkpoint blockade combination strategies in preclinical models

Approach	Combination target	Preclinical model	Experimental treatment	Outcome	Human study[a]
Stromal remodeling	Focal adhesion kinase (FAK)	KPC autochthonous mouse model	Gemcitabine with FAKinh and PD-1 Ab and CTLA-4 Ab	Improved survival	Yes NCT02546531 [12]
	CXCR4	KPC autochthonous mouse model	CXCR4inh and PD-1Ab	Reduced tumour growth	Yes NCT02826486 [49]
Myeloid compartment	CXCR2	KPC autochthonous murine model	mPD-1 Ab with CXCR2 SM (AZ13381758)	Extended survival, abrogated metastasis	Yes NCT02583477 [48]
	CD40	Subcut transplant KPC murine cells	Gemcitabine/ nab-paclitaxel with CD10 agonist Ab	Tumour regression, prolonged survival, maintained T cell memory	Yes NCT03214250 [83]
	CSF1R	KC-INK4A/ Arf Orthotopic transplant	Gemcitabine with CTLA-4 Ab, PD-1 Ab, and CSF1R Ab combo	Completely blocked tumour progression, 85% tumour regression	Yes NCT02777710 [46]
Radiotherapy	Radiotherapy with immune checkpoint blockade	Subcut transplant KPC murine cells	CTLA-4 Ab, PD-1 Ab, and radiation triple combination	Prolonged survival	Yes NCT02311361 [84]
	Radiotherapy with CD40	Subcut and orthotopic transplant KPC murine cells	Radiation, CTLA-4 Ab, PD-1 Ab, and CD40 agonist Ab	Prolonged survival, increased abscopal effect	No

[a]Numbers indicate ClinicalTrials.gov identifier

20.3.1.2 Radiotherapy

Radiotherapy has a role in the neoadjuvant setting and for management of LAPC, and therefore combination with immune checkpoint blockade may be a promising strategy for PDAC. An abscopal effect exists, where radiotherapy induces an immune response that mediated regression of metastatic lesions lying outside the radiation fields. Radiotherapy could therefore activate the immune system, increase T-cell tumour trafficking and potentially elicit an anti-tumour response following immune checkpoint blockade. Initial evidence for synergism has been seen in PDAC possibly related to increased immunogenicity [40]. By increasing tumour visibility radiotherapy may synergise with immune therapy. Optimisation of radiation dose and timing along with the identification of potential biomarkers is likely to further enhance clinical effectiveness.

20.3.2 Combining Immune Checkpoint Inhibitors with Targeted Therapies

Combination rather than single agent strategies will likely dominate the clinical trial landscape (Fig. 20.1). While this argument is encouraging, and may benefit subgroups of patients, each of these groups are likely to be small. In order to expand the positive impact of immunotherapeutics in PDAC, wider strategies are necessary. Multi-targeted strategies aim to stimulate T-cell anti-tumour responses through a combination of chemotherapy, immune targeting of CD40 and immune checkpoint blockade. Others aim to combine immune checkpoint blockade with strategies to inhibit immunosuppression mediated by matrix proteins (hyaluronidase), fibroblasts (FAK1), and myeloid cell populations (CSF1R, CXCR2, CCR2, BTK).

Further strategies for Immunotherapeutics in development include targeting indolemine 2,3-deoxygenade (IDO), a tryptophan-catabolizing enzyme that, when activated via tumours or another inflammatory stimulus, activates suppressive activity in dendritic cells leading to Treg activation. A recent phase II study of metastatic PDAC testing gemcitabine plus nab-paclitaxel in combination with indoximod revealed treatment responders with evidence of increased $CD8^+$ T-cell density in on-treatment biopsies [41]. Interestingly, $FOXP3^+$ was upregulated in responders and non-responders suggesting chemotherapy alone influences the immune landscape. This presents implications for the allocation of immunotherapy according to subtype stratifications of PDAC [42]. Despite these data encouraging data, PDL1 blockade in combination small molecule inhibition of IDO in unselected PDAC patients failed to achieve objective responses [43].

CD40 is a TNF receptor superfamily member that is expressed by many cells, including B cells, monocytes, endothelial cells, and fibroblasts. CD40 agonists have been shown to activate APCs and promote tumour regression, and synergize with gemcitabine in mice to increase intratumoural effector T-cell infiltration and induce

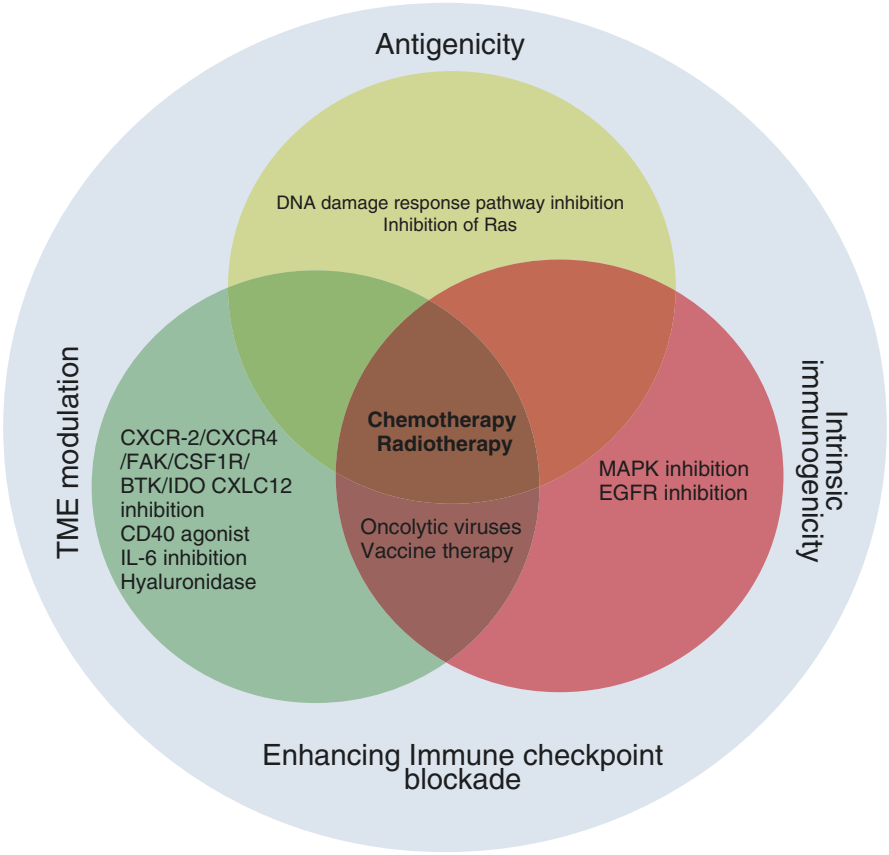

Fig. 20.1 Combination strategies to enhance immune checkpoint blockade efficacy. Ultimately synergism of all three aspects will likely be most successful

T-cell–dependent PDAC tumour regression [29] and are subject to testing in clinical trials [44].

Alternatively, immunotherapy strategies may condition the immune landscape to enhance responsiveness to traditional chemotherapy. In locally advanced PDAC, inhibition of CCR2, a chemokine receptor involved in the recruitment of immunosuppressive TAMs in combination with gemcitabine and nab-paclitaxel have been successful in disrupting immune cell recruitment to tumours with promising results [45].

Another receptor for which inhibition depletes macrophages, is colony-stimulating factor-1 receptor (CSF1R), Inhibition of which increased expression of checkpoint molecules on PDAC tumour cells and T-cells, and when synergized with immune checkpoint blockade and gemcitabine, further slowed murine PDAC growth [46]. In a further GEMM PDAC model, CSF1R inhibition, resulted in shrinkage of established tumours and increased mouse survival [47]. Along with diminished malignant T-cell proliferation, and increased cell death there was an

enhanced T-cell response. In addition to the loss of macrophages and rewiring of multiple TME features, there was evidence global changes in gene expression akin to switching PDAC subtypes.

Recently, it has been demonstrated that inhibition of a key mediator of neutrophil migration C-X-C Motif Chemokine Receptor 2 (CXCR2) enhances T-cell infiltration through inhibiting neutrophil/myeloid-derived suppression of T-cell recruitment in a GEMM, and is effective in increasing survival in combination with immune checkpoint blockade (Fig. 20.2) [48]. Peptide inhibitor, but not germline deletion of Cxcr2, improved survival, revealing differential effects in early and late tumours. Subsequently this strategy has been translated into a clinical trial in the metastatic setting (NCT02583477).

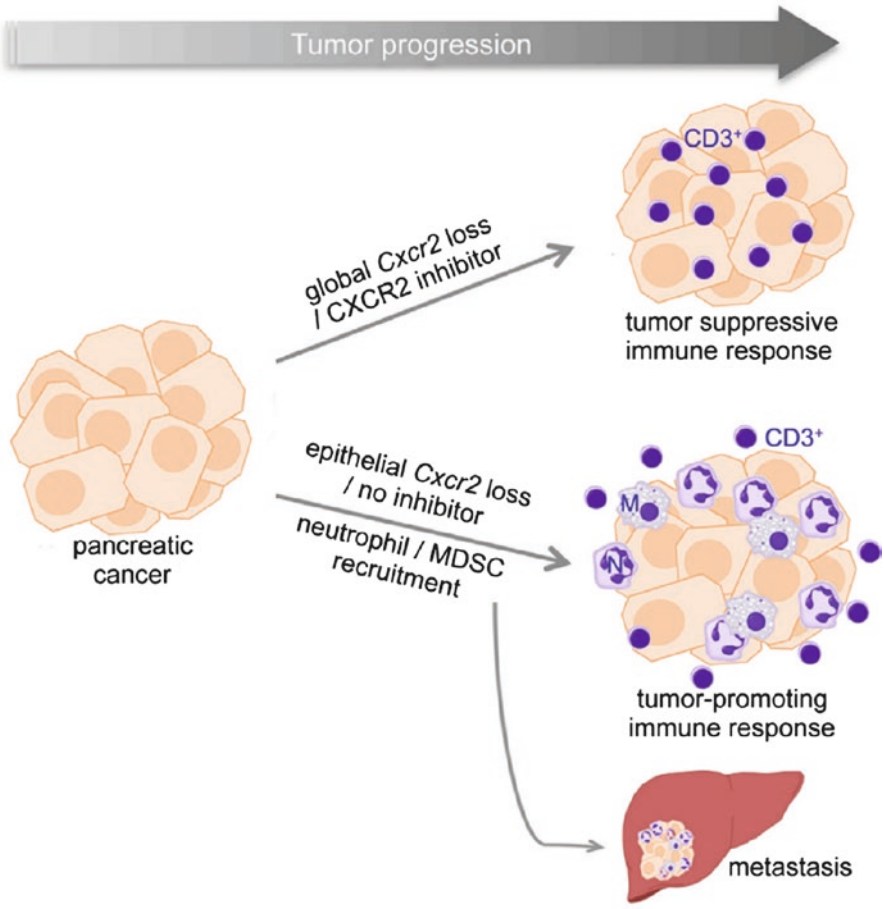

Fig. 20.2 Myeloid derived suppressor cells are important immune modulation targets in pancreatic cancer. Neutrophils/MDSCs play a key role in the establishment of the metastatic niche. CXCR2 has been shown to be important in immune modulation of pancreatic cancer with inhibition of CXCR2 demonstrated to enhance T-cell entry, reduce metastasis and improve response to gemcitabine and anti-PD1 in a murine model. (Image reproduced from Steele et al. Cancer Cell Volume 29, Issue 6, 13 June 2016, Pages 832–845)

CXCR4, a chemokine receptor whose expression in human pancreatic tissues is associated with a poorer prognosis. Inhibiting CXCR4 synergized with immune checkpoint blockade to decrease tumour size in a murine model [49], which has prompted an assessment in clinical trials (NCT02826486, NCT02907099)

Thus, multiple elements exist within the TME which may serve to switch PDAC from an immunologically impervious to sensitive phenotype. Indeed, evidence may suggest that switching of transcriptomic phenotypes may also be a potential strategy to achieve this goal [50].

20.3.2.1 Sequencing of Chemotherapy and Immunotherapies

In the management of human PDAC, the optimal sequencing of chemotherapy and immunotherapies is undecided, partly as our understanding of the immune landscape is predicated on analysis of a select subgroup of early-stage resected tumours, yet the majority of clinical trials are focussed on management of metastatic disease. In the clinic, patients will often receive multiple rounds of chemotherapy prior to receipt of immunotherapeutics. This has the potential of mitigating the maintenance of anti-tumour immune response by ablating proliferating immune cells and stimulating senescence of T-cells. Concurrent administration of chemotherapy and immunotherapy may be impactful in pre-clinical cancer models however, it is not clear whether this strategy is optimal in the clinical setting [51]. Myelosuppression may result from chemotherapy, and while this may be of benefit in terms of facilitating T-cell entry, it may also negatively impact efficacy of immune targeting approaches to readdress MDSC activity [48, 52]. Alternatively, treatment sequencing the immunotherapeutic following chemotherapy induction as reported in NSCLC [53] may be an option in PDAC in combination with PARP inhibition following completion of platinum chemotherapy, as a maintenance strategy prior to evidence of disease progression.

20.4 Other Immunotherapeutic Approaches

Given the effectiveness of checkpoint blockade in other cancers, investigators have begun to explore the potential of further manipulations of T-cell responses against tumour antigens. Below we explore techniques to augment T-cell responses in the form of vaccination, CAR-T cell therapies and other factors that may influence the efficacy of harnessing the immune system against PDAC.

20.4.1 Targeting Tumour Antigens in PDAC

The utility of immunotherapy depends upon presence and detection of immunogenic tumour antigens by T cells. Ideally, such tumour antigens are selectively expressed on cancer cells. Antigens are derived from either: (a) differential

cancer-cell expression; or (b) result from mutations or rearrangements in genetic sequences generating neoepitopes (mutational neoantigens).

Patients with microsatellite unstable tumours are a rare entity in pancreatic cancer (approximately 2%) [54]. These tumours exhibit response to immune checkpoint blockade [24], suggesting progress in the treatment of PDAC including employment of immunotherapies will require precision selection of patients. The mutational burden in tumours with microsatellite instability is greatly increased in PDAC [55]. Interestingly, exceptional patients with recalcitrant PDAC with microsatellite stable tumours have exhibited response to immune checkpoint blockade when combined with CSF1R inhibition [56]. Pre-clinical models have shown that [47] targeting macrophages within the tumour microenvironment releases resistance of these tumours to this approach.

20.4.2 Tumour Associated Antigens as Targets for PDAC Immunotherapy

Tumour associated antigens have received most attention as targets for PDAC immunotherapy due to the potential to treat multiple patients with the same therapy. Epidermal growth factor receptor (HER/EGFR/ERBB) family proteins and mesothelin [57] are examples of therapeutic targets under clinical investigation in PDAC. However, because of multiple sites of expression, off target effects occur.

It is accepted that as with other tumours, PDAC with higher mutational loads generate more neoantigens [58]. While initially no clear correlation between neoantigen load, activated T-cell infiltrate and outcome for patients with PDAC was observed, more recent examinations demonstrated heterogeneity in intratumoural T-cell infiltrates, with neoantigens potentially serving as targets for a subgroup of T-cells [17]. Supporting this fact, those tumours with evidence of mismatch repair or DNA damage repair signature have evidence of adaptive immune activation and evidence of a higher neoantigen load [59]. In patients with prolonged survival following resection for PDAC, neoantigens have been identified as T-cell targets, with those tumours demonstrating a >10-fold density of cytolytic $CD8^+$ T-cells [17]. Additionally, a neoantigen quality fitness model, which integrated clonal genealogy, epitope homology and T-cell receptor affinity provided prognostic utility.

20.4.3 Vaccine Immunotherapy Strategies for PDAC

The lack of efficacy associated with monotherapy immune checkpoint blockade in human PDAC suggests that strategies are necessary to activate or prime components of the immune TME in particular tumour-specific T-cells. Despite promise, efforts to vaccinate against Kras positive cells in patients with PDAC have been limited to only a small series of trials which have failed to show durable benefit [60, 61]. Other strategies to target Kras are being considered, however, it is likely that the complex

nature of the pancreatic TME is not determined solely by the near ubiquitous Kras mutation present in the disease.

Further, vaccine strategies including irradiated autologous tumour cells (GVAX), live attenuated bacteria expressing mesothelin (CRS-207) and peptide-based vaccines have all failed to date to demonstrate clinical benefit [62–64].

However, there is evidence from resected specimens that for some patients the immune landscape can be perturbed by vaccines. In the setting of a GM-CSF gene-transfected irradiated allogenic whole tumour cell vaccine, GVAX, tertiary lymphoid aggregates were identified and associated with prolonged survival in surgically resected disease [65].

Additionally, GVAX impact appears to extend to the PDAC TME with evidence of increased T-cell infiltrations and myeloid activation [66]. Augmentation of GVAX activity has been achieved through combination of cyclophosphamide at low dose with enhanced anti-tumour activity [67] and the detection of tumour-specific T-cells in the peripheral blood [68]. An expansion of a diverse mesothelin-specific T-cell repertoire has been recorded in some patients who have responded to Cy/GVAX/CRS-207, a feature that was associated with improved survival [64]. These exploratory studies support the rationale for combining vaccines with immune checkpoint blockade in an effort to both prime T-cells and perturb immune mechanisms which may limit T-cell effector activity.

The limited impact of immunotherapeutic strategies in PDAC has generated the concern that PDAC is immunologically ‘cold’. Yet, the preclinical studies and response to vaccines therapies suggests that this immunological inertness may indeed be flexible [65].

20.4.4 Augmenting T-Cell Responses: CAR-T-Cells

The strategy of adoptive cell therapy aims to removes the need for endogenous T-cell responses and facilitate an environment for the study of the anti-tumour potential of tumour-reactive T-cells. While for acute lymphoblastic leukaemia, Chimeric antigen receptor (CAR)-T-cells directed against CD19 have generated noteworthy responses, for patients with PDAC clinical improvement have yet to be realised [69]. To date, in murine models CAR-T-cells targeting CEA, Her2/neu and CD24 induced destruction of antigen-positive cells [70]. In human PDAC CARs targeting mesothelin, have demonstrated T-cell trafficking to the tumour site with transient partial responses without on-target, off-tumour toxicity [71]. This therapeutic strategy is limited by the quality and uniformity of antigen targets, with the potential to impact PDAC dependent on the capacity to generate productive polyfunctional endogenous T-cell responses and will ultimately require combinatorial approaches [72]. Especially challenging is the high number of infiltrating Tregs and MDSCs associated with the PDAC TME, capable of deactivating CAR-T cells via inhibitory cytokines.

20.4.5 Selecting Patients with PDAC for Onco-Immunology Strategies

Only a subset of PDAC patients respond to immune checkpoint blockade strategies, and optimization of patient selection for treatment is imperative. Therapy outcome is determined at various levels:

1. The degree of tumour "foreignness," as reflected by mutational burden and expression of viral genes.
2. The composition and activity of a pre-existing immune infiltrate.
3. Mechanisms of tumour escape from immune surveillance.

PD-L1 protein expression is used in NSCLC to select patients who benefit from frontline PD-1 inhibitor immunotherapy ahead of chemotherapy [73]. Genomic and transcriptomic profiling have proven capable of identifying patients who failed to respond to immune checkpoint blockade [74]. As part of studies undertaken through the International Cancer Genome Consortium (ICGC), four transcriptomic subtypes of primary untreated PDAC were identified with definition of candidate immune avoidance mechanisms that could potentially be targeted with existing and emerging therapeutics if appropriately combined and directed towards selected patients [42]. The 'immunogenic subtype' was defined by enrichment for pathways involved in immune cell infiltration and immune avoidance mechanisms. Evidence of infiltrating cytotoxic $CD8^+$ T-cells and regulatory T and B-cells, along with expression of CTLA-4 and PD-1 immune checkpoint pathways, suggests immune suppression in these tumours may be potentially targetable with immune checkpoint blockade. These subtyping data may explain why initial human clinical trials of mono-immunotherapy failed in PDAC. This profiling strategy would have the advantage of being able to determine a tumour's immunogenicity upfront, before treatment commences.

20.4.6 Influence of Microbiota on Onco-Immunology

Recently the role of microbiota in the initiation and maintenance of the immunosuppressive TME has received attention adding further to the complexity of immunotherapy response. In melanoma, a diverse microbial configuration was shown to predict a favourable immunotherapy response [75, 76], while in advanced renal and NSCLC microbial ablation impaired immune checkpoint blockade [77]. Notably in PDAC, targeting the microbiome has potential to facilitate immune checkpoint blockade [78], while a diverse intra-tumoural microbiome signature was prognostic in multiple patient cohorts [79] suggesting that ultimately consideration of the microbiome-immune cell compartments have potential to inform immunotherapeutic decisions for PDAC patients [80].

20.4.7 Optimising Onco-Immunology Integration in PDAC

While generally well tolerated, the introduction of immunotherapies to PDAC management may result in an array of toxicities not normally encountered with standard chemotherapeutics [81]. Therefore, caution must be employed to ensure that strategies which provide no benefit or cause harm, fail rapidly, while simultaneously determining translational correlative that inform adaptation of treatment plans. Unsuccessful clinical trials may still yield important insights into mechanisms of resistance. Furthermore, the attenuation of the immune system risks accelerating disease progression as observed in a subset of NSCLC patients managed with immune checkpoint blockade [82].

20.5 Conclusions

PDAC remains an unforgiving and lethal cancer, with a mortality rate approaching its incidence rate, therefore novel strategies, to augment often poorly tolerated chemotherapies, are necessary. The success apparent in other recalcitrant cancers suggests that a subgroup of patients with PDAC may benefit from onco-immunology strategies and that others have potential to be converted to responders. While PDAC lacks high tumour mutational burden and demonstrates generally low levels of T-cell density, T-cell tumour recognition is associated with more favourable survival. Moreover, immune checkpoint blockade has demonstrated impact in that subgroup of patients with PDAC who demonstrate microsatellite instability.

Multiple redundant barriers to immunotherapies within the milieu of the PDAC TME must be overcome through a combinatorial strategy of novel agents targeting the immune landscape, along with the stroma, in concert with standard and novel therapies. We look forward to preclinical models targeting the immune system in PDAC translating to human trial platforms which will inform both treatment responses and failures, providing insights into compensatory mechanisms of resistance. In the context of improved outcomes associated with platinum based FOLFIRINOX in localised and metastatic disease, combination therapy, including strategies to boost adaptive immunity, break systemic tolerance, and increase tumour immunogenicity has potential to revolutionize PDAC treatment.

References

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74:2913–21.
2. Zheng L, Xue J, Jaffee EM, et al. Role of immune cells and immune-based therapies in pancreatitis and pancreatic ductal adenocarcinoma. Gastroenterology. 2013;144:1230–40.

3. Steele CW, Karim SA, Foth M, et al. CXCR2 inhibition suppresses acute and chronic pancreatic inflammation. J Pathol. 2015;237:85–97.
4. Collins MA, Bednar F, Zhang Y, et al. Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest. 2012;122:639–53.
5. Guerra C, Schuhmacher AJ, Canamero M, et al. Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell. 2007;11:291–302.
6. Steele CW, Jamieson NB, Evans TR, et al. Exploiting inflammation for therapeutic gain in pancreatic cancer. Br J Cancer. 2013;108:997–1003.
7. Vennin C, Murphy KJ, Morton JP, et al. Reshaping the tumor stroma for treatment of pancreatic cancer. Gastroenterology. 2018;154:820–38.
8. Hwang RF, Moore T, Arumugam T, et al. Cancer-associated stromal fibroblasts promote pancreatic tumor progression. Cancer Res. 2008;68:918–26.
9. Ozdemir BC, Pentcheva-Hoang T, Carstens JL, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell. 2014;25:719–34.
10. Catenacci DV, Junttila MR, Karrison T, et al. Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J Clin Oncol. 2015;33:4284–92.
11. Olive KP, Jacobetz MA, Davidson CJ, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009;324:1457–61.
12. Jiang H, Hegde S, Knolhoff BL, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat Med. 2016;22:851–60.
13. Miller BW, Morton JP, Pinese M, et al. Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: inhibition of LOX abrogates metastasis and enhances drug efficacy. EMBO Mol Med. 2015;7:1063–76.
14. Hingorani SR, Harris WP, Beck JT, et al. Phase Ib study of PEGylated recombinant human hyaluronidase and gemcitabine in patients with advanced pancreatic cancer. Clin Cancer Res. 2016;22:2848–54.
15. Vennin C, Melenec P, Rouet R, et al. CAF hierarchy driven by pancreatic cancer cell p53-status creates a pro-metastatic and chemoresistant environment via perlecan. Nat Commun. 2019;10:3637.
16. Li J, Byrne KT, Yan F, et al. Tumor cell-intrinsic factors underlie heterogeneity of immune cell infiltration and response to immunotherapy. Immunity. 2018;49:178–193.e7.
17. Balachandran VP, Luksza M, Zhao JN, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017;551:512–6.
18. Clark CE, Hingorani SR, Mick R, et al. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. Cancer Res. 2007;67:9518–27.
19. Liu L, Zhao G, Wu W, et al. Low intratumoral regulatory T cells and high peritumoral CD8(+) T cells relate to long-term survival in patients with pancreatic ductal adenocarcinoma after pancreatectomy. Cancer Immunol Immunother. 2016;65:73–82.
20. Daley D, Zambirinis CP, Seifert L, et al. gammadelta T cells support pancreatic oncogenesis by restraining alphabeta T cell activation. Cell. 2016;166:1485–1499.e15.
21. McAllister F, Bailey JM, Alsina J, et al. Oncogenic Kras activates a hematopoietic-to-epithelial IL-17 signaling axis in preinvasive pancreatic neoplasia. Cancer Cell. 2014;25:621–37.
22. Zhang Y, Velez-Delgado A, Mathew E, et al. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut. 2017;66:124–36.
23. Farren MR, Mace TA, Geyer S, et al. Systemic immune activity predicts overall survival in treatment-naive patients with metastatic pancreatic cancer. Clin Cancer Res. 2016;22:2565–74.
24. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409–13.
25. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018–28.

26. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–32.
27. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33:828–33.
28. Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;14:399–416.
29. Beatty GL, Winograd R, Evans RA, et al. Exclusion of T cells from pancreatic carcinomas in mice is regulated by Ly6C(low) F4/80(+) extratumoral macrophages. Gastroenterology. 2015;149:201–10.
30. Ino Y, Yamazaki-Itoh R, Shimada K, et al. Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer. Br J Cancer. 2013;108:914–23.
31. Gunderson AJ, Kaneda MM, Tsujikawa T, et al. Bruton tyrosine kinase-dependent immune cell cross-talk drives pancreas cancer. Cancer Discov. 2016;6:270–85.
32. Pylayeva-Gupta Y, Das S, Handler JS, et al. IL35-producing B cells promote the development of pancreatic neoplasia. Cancer Discov. 2016;6:247–55.
33. Galluzzi L, Buque A, Kepp O, et al. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell. 2015;28:690–714.
34. Zitvogel L, Galluzzi L, Smyth MJ, et al. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity. 2013;39:74–88.
35. Eriksson E, Wenthe J, Irenaeus S, et al. Gemcitabine reduces MDSCs, tregs and TGFbeta-1 while restoring the teff/treg ratio in patients with pancreatic cancer. J Transl Med. 2016;14:282.
36. Di Caro G, Cortese N, Castino GF, et al. Dual prognostic significance of tumour-associated macrophages in human pancreatic adenocarcinoma treated or untreated with chemotherapy. Gut. 2016;65:1710–20.
37. Bohm S, Montfort A, Pearce OM, et al. Neoadjuvant chemotherapy modulates the immune microenvironment in metastases of tubo-ovarian high-grade serous carcinoma. Clin Cancer Res. 2016;22:3025–36.
38. Homma Y, Taniguchi K, Nakazawa M, et al. Changes in the immune cell population and cell proliferation in peripheral blood after gemcitabine-based chemotherapy for pancreatic cancer. Clin Transl Oncol. 2014;16:330–5.
39. Shibuya KC, Goel VK, Xiong W, et al. Pancreatic ductal adenocarcinoma contains an effector and regulatory immune cell infiltrate that is altered by multimodal neoadjuvant treatment. PLoS One. 2014;9:e96565.
40. Azad A, Yin Lim S, D'Costa Z, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy. EMBO Mol Med. 2017;9:167–80.
41. Bahary N, Wang-Gillam A, Haraldsdottir S, et al. Phase 2 trial of the IDO pathway inhibitor indoximod plus gemcitabine/nab-paclitaxel for the treatment of patients with metastatic pancreas cancer. J Clin Oncol. 2018;36:abstr 4015.
42. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531:47–52.
43. Naing A, Powderly J, Falchook G, et al. Abstract CT177: Epacadostat plus durvalumab in patients with advanced solid tumors: preliminary results of the ongoing, open-label, phase I/II ECHO-203 study [abstract]. Cancer Res. 2018;78:CT177.
44. Beatty GL, Torigian DA, Chiorean EG, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clin Cancer Res. 2013;19:6286–95.
45. Nywening TM, Wang-Gillam A, Sanford DE, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. Lancet Oncol. 2016;17:651–62.
46. Zhu Y, Knolhoff BL, Meyer MA, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer Res. 2014;74:5057–69.

47. Candido JB, Morton JP, Bailey P, et al. CSF1R(+) macrophages sustain pancreatic tumor growth through T cell suppression and maintenance of key gene programs that define the squamous subtype. Cell Rep. 2018;23:1448–60.
48. Steele CW, Karim SA, Leach JDG, et al. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell. 2016;29:832–45.
49. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci U S A. 2013;110:20212–7.
50. Collisson EA, Bailey P, Chang DK, et al. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019;16:207–20.
51. Pfirschke C, Engblom C, Rickelt S, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. Immunity. 2016;44:343–54.
52. Long KB, Gladney WL, Tooker GM, et al. IFNgamma and CCL2 cooperate to redirect tumor-infiltrating monocytes to degrade fibrosis and enhance chemotherapy efficacy in pancreatic carcinoma. Cancer Discov. 2016;6:400–13.
53. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377:1919–29.
54. Lupinacci RM, Goloudina A, Buhard O, et al. Prevalence of microsatellite instability in intraductal papillary mucinous neoplasms of the pancreas. Gastroenterology. 2018;154:1061–5.
55. Humphris JL, Patch AM, Nones K, et al. Hypermutation in pancreatic cancer. Gastroenterology. 2017;152:68–74.e2.
56. Wainberg Z, Piha-Paul S, Luke J, et al. First-in-human phase 1 dose escalation and expansion of a novel combination, anti-CSF-1 receptor (cabiralizumab) plus anti-PD-1 (nivolumab), in patients with advanced solid tumors. Immunother Cancer. 2017; https://doi.org/10.13140/RG.2.2.28962.53443.
57. Le DT, Brockstedt DG, Nir-Paz R, et al. A live-attenuated Listeria vaccine (ANZ-100) and a live-attenuated Listeria vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. Clin Cancer Res. 2012;18:858–68.
58. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491:399–405.
59. Connor AA, Denroche RE, Jang GH, et al. Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma. JAMA Oncol. 2017;3:774–83.
60. Weden S, Klemp M, Gladhaug IP, et al. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. Int J Cancer. 2011;128:1120–8.
61. Melero I, Gaudernack G, Gerritsen W, et al. Therapeutic vaccines for cancer: an overview of clinical trials. Nat Rev Clin Oncol. 2014;11:509–24.
62. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol. 2014;15:829–40.
63. Coveler AL, Rossi GR, Vahanian NN, et al. Algenpantucel-L immunotherapy in pancreatic adenocarcinoma. Immunotherapy. 2016;8:117–25.
64. Le DT, Wang-Gillam A, Picozzi V, et al. Safety and survival with GVAX pancreas prime and Listeria monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J Clin Oncol. 2015;33:1325–33.
65. Lutz ER, Wu AA, Bigelow E, et al. Immunotherapy converts nonimmunogenic pancreatic tumors into immunogenic foci of immune regulation. Cancer Immunol Res. 2014;2:616–31.
66. Tsujikawa T, Kumar S, Borkar RN, et al. Quantitative multiplex immunohistochemistry reveals myeloid-inflamed tumor-immune complexity associated with poor prognosis. Cell Rep. 2017;19:203–17.
67. Ercolini AM, Ladle BH, Manning EA, et al. Recruitment of latent pools of high-avidity CD8(+) T cells to the antitumor immune response. J Exp Med. 2005;201:1591–602.

68. Laheru D, Croghan G, Bukowski R, et al. A phase I study of EKB-569 in combination with capecitabine in patients with advanced colorectal cancer. Clin Cancer Res. 2008;14:5602–9.
69. Brown CE, Mackall CL. CAR T cell therapy: inroads to response and resistance. Nat Rev Immunol. 2019;19:73–4.
70. Maliar A, Servais C, Waks T, et al. Redirected T cells that target pancreatic adenocarcinoma antigens eliminate tumors and metastases in mice. Gastroenterology. 2012;143:1375–1384.e5.
71. Beatty GL, O'Hara MH, Lacey SF, et al. Activity of mesothelin-specific chimeric antigen receptor T cells against pancreatic carcinoma metastases in a phase 1 trial. Gastroenterology. 2018;155:29–32.
72. Majzner RG, Mackall CL. Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med. 2019;25:1341–55.
73. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823–33.
74. Jamieson NB, Maker AV. Gene-expression profiling to predict responsiveness to immunotherapy. Cancer Gene Ther. 2017;24:134–40.
75. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science. 2018;359:104–8.
76. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359:97–103.
77. Derosa L, Hellmann MD, Spaziano M, et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol. 2018;29:1437–44.
78. Pushalkar S, Hundeyin M, Daley D, et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov. 2018;8:403–16.
79. Riquelme E, Zhang Y, Zhang L, et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell. 2019;178:795–806.e12.
80. Vitiello GA, Cohen DJ, Miller G. Harnessing the microbiome for pancreatic cancer immunotherapy. Trends Cancer. 2019;5:670–6.
81. Sanchez K, Page DB, Urba W. Immunotherapy toxicities. Surg Oncol Clin N Am. 2019;28:387–401.
82. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. JAMA Oncol. 2018;4:1543–52.
83. Byrne KT, Vonderheide RH. CD40 stimulation obviates innate sensors and drives T cell immunity in Cancer. Cell Rep. 2016;15:2719–32.
84. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520:373–7.

Chapter 21
Molecular Subtyping of Pancreatic Cancer

Stephan B. Dreyer, Nigel B. Jamieson, David K. Chang, and Andrew V. Biankin

Take Home Messages

- Considerable inter-tumoral heterogeneity exists in pancreatic cancer.
- Transcriptomic molecular subtyping has identified two broad subtypes: *Squamous* and *Classical*.
- Squamous tumours are associated with a poorer survival demonstrating evidence of epithelial-to-mesenchymal transition and association with adenosquamous morphology.
- Classical progenitor is associated with better survival, pancreatic endodermal differentiation and IPMN-derived pancreatic cancer.

Pearls and Pitfalls

- Comparing molecular subtype-classifiers between different studies is limited by variability of inputs, gene expression technology used and tissue preparation techniques.
- There remains an ongoing debate on whether an endocrine (ADEX) subtype of pancreatic cancer exists.
- Molecular subtyping can potentially select patients for surgery, but clinical outcomes will also be largely affected by response to systemic therapy, particularly in the neoadjuvant setting.

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Future Perspectives
- To determine if molecular subtyping can be determined from preoperative biopsies.
- To determine if molecular subtyping can inform therapeutic development and predict response to systemic therapies.
- To determine the extent of subtype intra-tumoural heterogeneity and its effect on treatment response and prognostication.

21.1 Introduction

Molecular subtyping of cancer has now been performed for the majority of common cancers following seminal studies in lymphoma and breast cancer [1, 2]. Using clustering techniques based on mRNA gene expression, unbiased molecular associations between individual cancers can be identified and clustered together in order to form relevant reproducible subgroups that are not influenced by user selection. This allows for sensible analyses of commonly altered gene expression patterns amongst subgroups, which has the potential to facilitate therapeutic and biomarker development.

In this chapter, we describe the differences between molecular subtypes of pancreatic cancer, focusing specifically on pancreatic ductal adenocarcinoma, and potential implications for the surgical management of pancreatic cancer.

21.2 Subtyping Pancreatic Cancer from Gene Expression

There have been, to date, a number of studies aimed at subtyping pancreatic cancer based on large scale mRNA expression. Various technologies have been used, including gene expression arrays, but now it is mostly performed using RNA sequencing (RNAseq) (Table 21.1). These have used differing inputs, including bulk tumours, patient derived xenografts and cell lines [3–6]. The differences in sample origin and preparation (bulk tumour vs epithelial micro dissection) has

Table 21.1 Techniques for gene expression analysis

Microarray	RNAseq
Measures relative intensity	Measures number of sequencing reads
Hybridisation to known transcript probes	*Next generation sequencing and alignment of sequenced reads*
Low sensitivity Low dynamic range Can only sequence known transcripts No splicing/fusion information Low costs	High sensitivity Novel transcripts can be sequenced Can detect structural variations and splicing Can detect gene fusions Wider range of analytical tools Unlimited comparisons More expensive

contributed to some of the observed differences in subtypes and classifiers described to date [4–6]. In general, however, there is now consensus that two broad subtypes exist, termed Classical Pancreatic and Squamous (also known as basal) with differing molecular profiles but also clinical patterns of disease and behaviour [3]. The squamous or basal subtype is enriched for genes involved in squamous differentiation and will be from here on referred to as squamous subtype. This specifically relates to molecular subtyping and should not be confused with pancreatic cancer with adenosquamous histological features.

The largest characterisation of pancreatic cancer to date has been an integrated molecular analysis of the International Cancer Genome Consortium (ICGC) pancreatic cancer cohort led by the Australian Pancreatic Genome Initiative (APGI) [4, 7–10]. Bulk tumour specimens were used for RNA sequencing and analysis which identified four sub-types based on transcriptional networks that defines gene programs within the tumour epithelial component and the microenvironment [4]. Subtypes were termed squamous, pancreatic progenitor, aberrantly differentiated endocrine exocrine (ADEX) and immunogenic and correlated with histopathological findings and long-term outcomes [4]. The classical pancreatic subtype encompasses the pancreatic progenitor, ADEX and immunogenic subtypes and the subtle differences in these are described later on.

21.2.1 The Squamous (or Basal) Sub-Type

The squamous sub-type was so-called as it is enriched for gene programs described in squamous like tumours of breast, bladder, lung and head and neck cancer [11]. These co-segregated with histopathological adeno-squamous pancreatic cancer and gene programs associated with inflammation, hypoxia response, metabolic programming and TGF-β signalling [4]. MYC pathway activation was enriched in this sub-type and correlates with other studies demonstrating MYC activation in adenosquamous pancreatic cancer and poor outcome [4, 12, 13]. Hypermethylation and downregulation of genes involved in pancreatic endodermal differentiation (*PDX1*, *MNX1*, *GATA6*, *HNF1B*) appeared to contribute to loss of endodermal identity and epithelial to mesenchymal transition (EMT) [4]. Mutations in *KDM6A* and *TP53* was enriched in this cohort as seen in other squamous epithelial tumours, and this class was associated with poor survival in pancreatic cancer [14–16].

21.2.2 Classical Subtype

In contrast to the squamous sub-type, Bailey et al. described the pancreatic progenitor sub-type (termed from here on as classical pancreatic) which was associated with better survival and is primarily defined by pathways and networks involved in pancreatic endodermal differentiation [4]. The classical pancreatic subtype demonstrated increased expression of the apomucins *MUC1* and *MUC5AC*,

both associated with the pancreatico-biliary subtype of intra-ductal papillary mucinous neoplasms (IPMN) and was associated with invasive IPMN cancer histologically [4].

21.2.3 The Immunogenic Subtype

Due to the known influence of the stroma and microenvironment on pancreatic cancer biology [6, 17–23], the ICGC pancreatic cancer cohort was characterised deliberately using bulk tumour samples to include the molecular contribution of both the stromal and epithelial components of the tumour. Thus, the Bailey classification includes genes that were differentially expressed in the tumour microenvironment, which leads to the inclusion of an immunogenic subtype which is based on immune cell infiltrate in the tumour microenvironment [4]. The immunogenic subtype exhibited similar epithelial gene expression to the classical pancreatic subtype, with the addition of enrichment for genes involved in immune cell infiltration and associated immune signalling pathways [4]. Transcriptomic evidence of infiltrating cytotoxic $CD8^+$ T cells, regulatory T and B cells along with expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) immune checkpoint pathways suggests immune suppression that can be targeted with checkpoint blockade in this subgroup of pancreatic cancer [4]. Expression signatures of immune cells predicted outcome, specifically macrophage infiltration and T cell co-inhibition associated with poor survival after pancreatectomy [4].

A recent study by Puleo et al. demonstrated that by examining the transcripts from formalin fixed and paraffin-embedded pancreatic cancer that the squamous and classical pancreatic subtypes (which encompasses progenitor, ADEX and immunogenic) are recapitulated [19]. Immune infiltrates in the classical pancreatic subtype allowed stratification termed pure classical and immune classical [19]. The immune classical correlates with the immunogenic subtype described by Bailey et al. [4]. Furthermore, they describe two distinct stromal subtypes termed ‘stroma activated’ and ‘desmoplastic’ which demonstrated features of both the squamous and classical pancreatic subtypes [19]. These stromal features were not indiscernible from epithelial subtypes (classical and squamous) and were only present when lower epithelial samples were included, which makes it impossible to distinguish whether these are unique subsets or features of the classical and squamous subtypes [19].

Collisson et al. was the first to categorise pancreatic cancer with large scale gene expression data using hybridisation array-based mRNA expression from micro dissected pancreatic cancer epithelium [5]. This identified three subtypes, quasi-mesenchymal (QM-PDA), classical and exocrine subtypes [5]. The QM-PDA sub-group was associated with worse overall survival and overlaps with the squamous sub-type described by Bailey et al. [4, 5]. Collisson further described an endocrine sub-type that overlaps directly with the Bailey ADEX class [4, 5]. These were

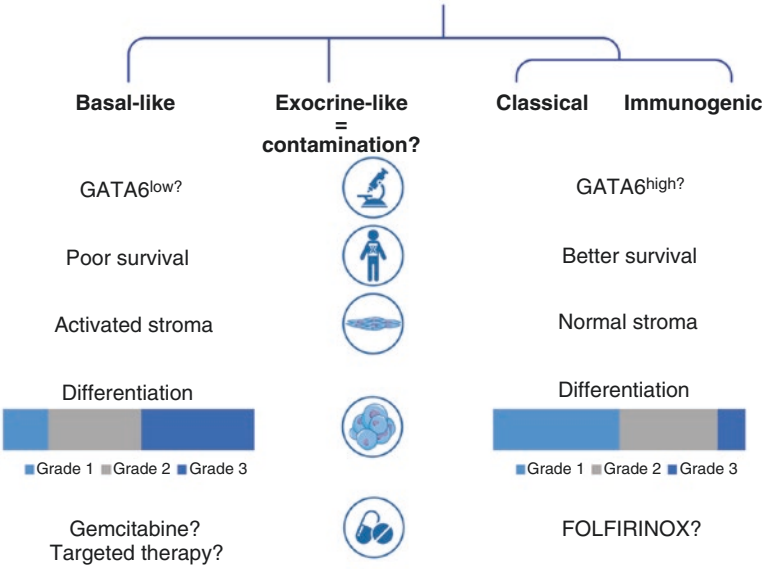

Fig. 21.1 Features of Molecular Subtypes of pancreatic cancer. A simplified phylotranscriptomic tree of pancreatic cancer. The squamous (or basal) subtype is associated with poor differentiation and activated stroma. The classical subtype (including immunogenic and ADEX) is associated with better survival and better tumour differentiation. The presence of the ADEX (or exocrine like) subtype remains debated and may reflect contamination from normal pancreas transcripts. (Used with permission from *Annals of Oncology*. 2019: 30 (9) [24])

enriched for gene programs in endocrine and exocrine development and appears to be a sub-group of the classical pancreatic subtype (Fig. 21.1) [4, 5].

Criticism of the ADEX and endocrine sub-groups suggest that these are defined by large amount of normal pancreas contamination in low cellularity tumours [6, 19, 25]. Puleo et al.'s study also found that tumours with low epithelial cellularity and high normal pancreatic contamination were enriched for transcripts found in normal pancreas [19]. The Cancer Genome Atlas' contribution to pancreatic cancer utilised 150 resected pancreatic cancer's and applied the subtyping algorithms published by Collisson, Moffit and Bailey [25]. Their study was enriched with low epithelial cellularity tumours (median cellularity 18% on pathology review) and found good correlation between the squamous, basal and quasimesenchymal subtypes [25]. They also found, as expected, strong association between lymphocytic infiltration and transcripts seen in the immunogenic subtype, demonstrating again that this subtype is secondary to immune infiltration [25]. They also demonstrate that the Collisson endocrine and Bailey ADEX subtypes are enriched by low epithelial cellularity tumours [25]. This would suggest that the ADEX (or endocrine) subtype is indeed secondary to high normal pancreas contamination. However, methylation patterns of the ADEX class correlates with other pancreatic cancers, and patient derived cell lines and xenografts demonstrate gene enrichment profiles

that fall within the ADEX class, suggesting this is a genuine feature of the tumour epithelium [4, 26, 27]. In fact, recent pre-clinical studies have shown that the molecular subtype can be switched from squamous to ADEX in mice after pharmacological intervention [18, 28]. In addition, comparing studies with different profiling technology (gene expression array vs. RNAseq) may not be comparable due to the thresholds involved in clustering algorithms. As such, there still remains ongoing debate on the presence or absence of an endocrine-like subtype of pancreatic cancer.

Using a different approach to profile pancreatic cancer from the Biankin and Collisson groups, Moffitt et al. performed virtual microdissection to differentiate the stromal and epithelial components of pancreatic cancer and minimize the confounding impact normal pancreatic tissue may confer [6]. In simple terms, this involves subtracting and excluding gene expression values that is seen in normal pancreas to minimise the effect of normal gene expression on mRNA clustering. They described two sets of gene programs that define either an activated or normal stroma [6]. The activated stroma was associated with a worse prognosis and enriched for genes previously associated with poor survival including *MMP9*, *MMP11* and Wnt family members [6]. Defining gene expression within the epithelial component revealed two epithelial sub-types, named basal and classical [6]. The classical subtype was associated with improved prognosis and overlapped with the Collisson classical and Bailey progenitor sub-types [4–6]. Comparing the basal with the quasi-mesenchymal subtype, described by Collisson et al., revealed that the quasi-mesenchymal classification considers gene programs from the basal epithelial and activated stroma classes described by Moffit et al. [5, 6].

The stroma and local immune response are strongly associated with outcome and response to therapy and classifying tumours purely on epithelial gene expression is unlikely to fully account for all molecular processes in the disease. This suggests that expression or transcriptomic classification should incorporate gene signatures from both the microenvironment and tumour epithelium to fully account for the molecular pathology of pancreatic cancer. The Collisson and Bailey classifiers incorporates key stromal, immune and epithelial elements that reflect tumour biology and prognosis and may have greater utility than a separate epithelial classifier.

A recent study has demonstrated that the broad molecular subtypes (classical pancreatic vs. squamous) associated with specific histological features [29]. The squamous (or basal) subtype associated with non-gland forming morphology, which forms part of the spectrum of poorly differentiated pancreatic cancer that includes histological adenosquamous pancreatic cancer [29]. This is in keeping with studies investigating spatial heterogeneity of pancreatic cancer, which demonstrate that areas with histological adenosquamous features express ‘squamous’ (or basal) gene sets, even if the tumour is largely classical subtype. The classical subtype is associated with gland-forming, better differentiated morphology [29]. This appears to include IPMN-associated pancreatic cancer, and to date no IPMN-associated cancers have been demonstrated to be of squamous molecular subtype. Whether this is due to inherent molecular factors that predetermine subtype, or whether the morphological features of IPMN-associated pancreatic cancer is lost during evolution to squamous subtype remains to be determined.

An attempt to classify pancreatic cancer based on metabolic subtypes have been performed using data from the TCGA, ICGC and COMPASS trial cohorts, amongst others, using mRNA expression [30, 31]. This demonstrated four subtypes based on genes involved in metabolic alterations, a hallmark of cancer. This demonstrated that glycolytic activity is a feature of the squamous subtype, particularly in the setting of joint *KRAS* and *MYC* amplification [31]. A cholesterogenic subtype was strongly associated with the classical pancreatic subtype, suggesting that these two subtypes rely on different fuels for tumour growth, invasion and possibly metastases [31–34]. This is of great significance since metabolic inhibitors targeting glycolysis and cholesterol synthesis are currently entering clinical trial, and this study again demonstrates the importance of personalised approach to early phase therapeutic testing to avoid negative trials in unselected patient groups.

21.3 Consensus Towards Molecular Subtyping of Pancreatic Cancer

Recently there has been a formal consensus held to align molecular subtyping of pancreatic cancer in order to interrogate and compare subtypes for the benefit of therapeutic development. Currently, it is accepted that two distinct transcriptomic subtypes exist with varying molecular and clinical features [3] (Fig. 21.2). It is now accepted that these are referred to as the *Squamous* (or basal) and *Classical* pancreatic (also known as pancreatic progenitor, which incorporates the ADEX and immunogenic classes) subtypes (Fig. 21.1).

21.4 Evolution of Molecular Subtypes

Recent data demonstrates that the two broad classifications (squamous or basal and classical) harbour further sub-clusters that have distinct gene expression profiles (Figs. 21.1 and 21.2) [35]. Using RNAseq data from both early and late stage pancreatic cancer, Chan-Seng-Yue et al. defined subgroups that were termed basal-A and -B and classical-A and -B. The most interesting findings from this study was that the squamous (basal) subtype was enriched in the metastatic setting, and that squamous tumours were almost completely absent in the locally advanced setting (Fig. 21.2) [35]. Furthermore, they found that both subtypes exist in the same tumour when performing single cell RNAseq, and that the predominant subtype can change depending on the stage of the disease or on chemotherapy response [35]. Their findings suggest that the classical subtype is the default pathway for pancreatic cancer. This data is further supported by a study that investigated the transcriptomic spatial heterogeneity of pancreatic cancer [13]. Using fresh frozen specimens from a warm autopsy cohort of both primary and metastatic tumours, along with multi-regional samples from resected pancreatic cancer, Hayashi et al. demonstrate

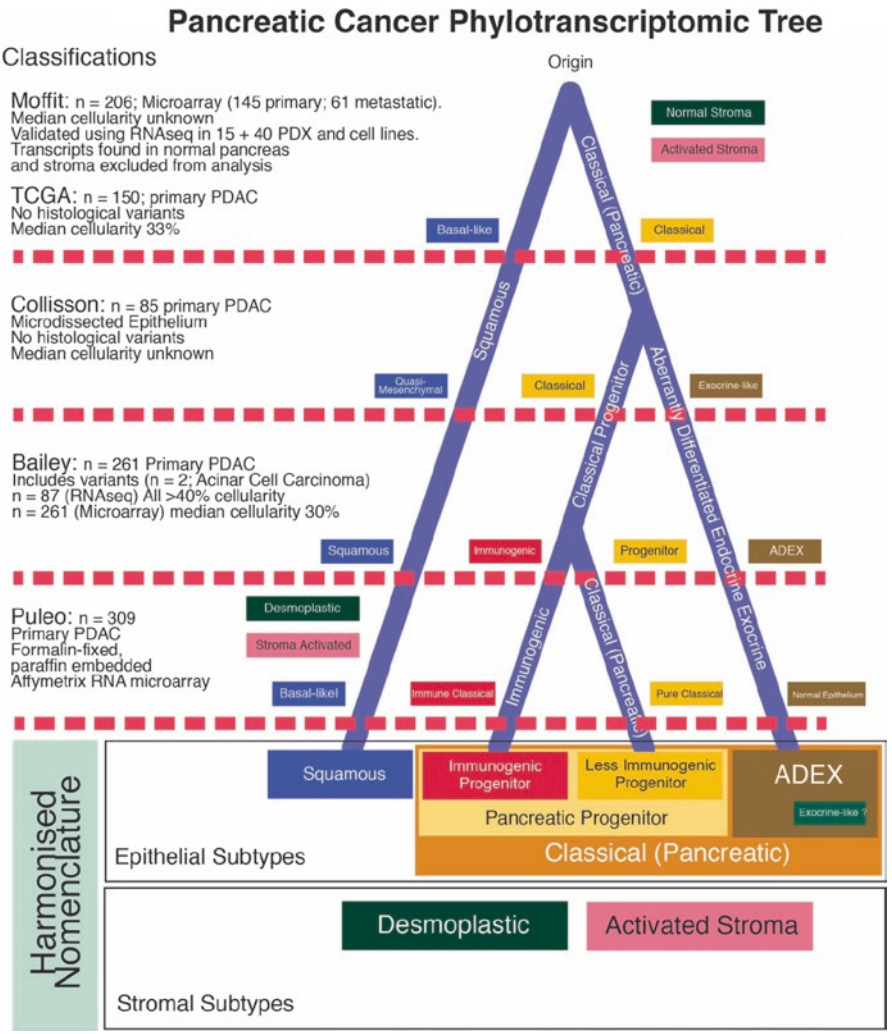

Fig. 21.2 Transcriptomic subtypes of pancreatic cancer. Incorporating the transcriptomic subtypes described by Moffit, Collisson and Bailey into a common nomenclature of molecular subtypes of pancreatic cancer. Two broad subtypes, the squamous and classical pancreatic exist. The classical pancreatic subtype can be further subdivided into a spectrum of tumours based on parallel lineages of pancreatic development. The exact relationship between stromal subtypes and epithelial subtypes have not been discerned and requires further investigation. However, as therapies targeting the tumour microenvironment develop, will likely play a role in future therapeutic development. (Used with permission from Collisson et al. [3])

that both squamous and classical pancreatic subtypes can exist in the same patient. By using organoid models to induce a squamous subtype, and clinical sample RNAseq data, their findings suggest that the squamous (or basal) subtype can arise on a background of classical pancreatic cancer, but not the other way around [13].

This suggests that the classical pancreatic subtype is the default evolutionary route for pancreatic cancer, and that epigenetic changes and mutations in chromatin modifiers and *MYC* amplification leads to squamous differentiation.

Our group interrogated the transcriptomes of patients with resected body and tail pancreatic cancer, in comparison with head and uncinate process pancreatic cancer [36]. We found that body and tail pancreatic cancer was more likely to be squamous and associated with loss of endodermal identity, enriched for epithelial to mesenchymal transition, inflammation and immune evasion [36]. Clinicians has long believed that the poor outcomes of body and tail pancreatic cancer compared to tumours of the head and uncinate process is in part due to late diagnosis as a result of the asymptomatic growth of these tumours with results from this particular cohort suggesting the same [37–40]. Firstly, tumours of the body and tail were larger in size which may reflect a biologically 'older' tumour. Secondly, body and tail pancreatic cancer correlated with molecular features that are driven by epigenetic events associated with chromosomal instability and epigenetic events that may drive intratumoral heterogeneity and an evolution towards the squamous subtype [41, 42]. The exact sequence of these events in tumorigenesis and progression have yet to be elicited but may be associated with a later stage of the disease evolution and suggest that the squamous subtype may be more advanced on the molecular clock (Figs. 21.2 and 21.3). What remains to be determined, is the underlying trigger for this evolution and why it is likely an early event in some patients, and late event in others.

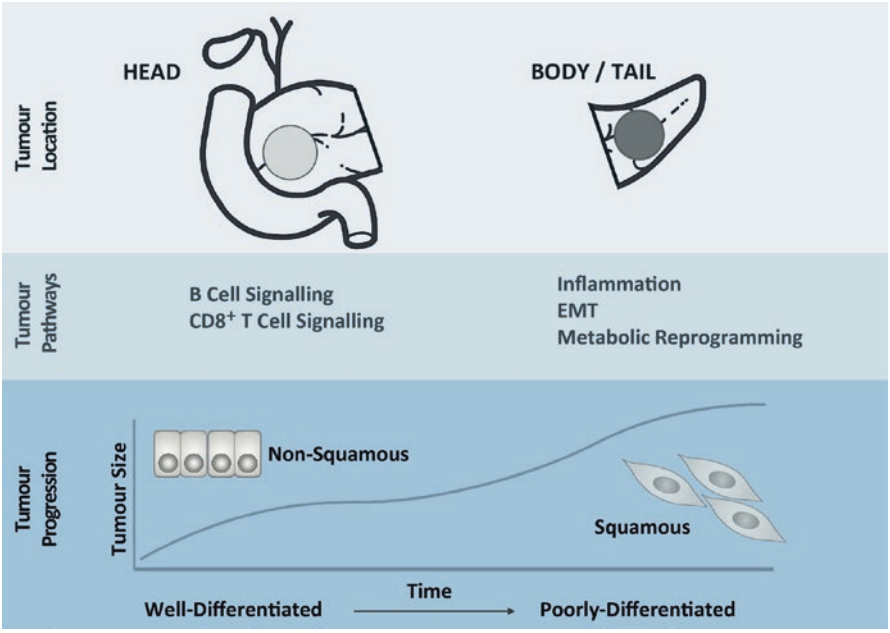

Fig. 21.3 Molecular pathology of body and tail pancreatic cancer. Body and tail pancreatic cancer was associated with transcriptional networks involved in tumour progression and metastases including pro-inflammatory gene expression, epithelial-to-mesenchymal transition and metabolic reprogramming. Histologically the squamous subtype is associated with poor differentiation (high grade) and reflects a later stage of tumour evolution. (Used with permission from Dreyer et al. [36])

Box 21.1 Next Generation Sequencing (NGS)
Sequencing technology that determines exact order of nucleotides in DNA or RNA sequence. NGS platforms perform massively parallel sequencing—millions of DNA fragments are sequenced in unison. Thus, can produce whole genome sequence in a matter of days.

This includes four key steps:

1. Library Preparation—DNA fragmented and barcoded
2. Clonal amplification—emulsion or bridge PCR, creates clusters of each DNA molecule
3. Sequence DNA molecules—different platforms use different technology. In basic terms, fluorescent labelled nucleotides are incorporated and imaged
4. Reads are re-assembled and mapped to a known genome

21.5 Is There a Role for Molecular Subtyping in Surgery for Pancreatic Cancer?

The wealth of molecular data that can be determined using *next generation sequencing* (Box 21.1) has led to molecular subtyping on a vast scale.

However, this only has clinical utility and significance if it leads to therapeutic development and improving patient selection for therapy (Fig. 21.4). The squamous subtype has been found to be associated with poor outcome in multiple studies [4–6, 36, 43, 44]. These, however, is largely confounded by the lack of clinical data in terms of stage, treatment pathways and patient selection—thus, making it difficult to draw conclusions from any clinical analyses. There has also been a multitude of studies aiming to develop prediction tools for selecting patients with good prognosis for surgical resection of pancreatic cancer [45–47]. These are not currently in clinical use in pre-operative selection, largely due to the requirement of post-operative variables to predict outcome. To address this we investigated the clinical utility of the expression of two molecules, S100A2 and S100A4, which functionally promote carcinogenesis and metastasis, as prognostic biomarkers in multiple independent cohorts of patients with resectable pancreatic cancer ($n = \sim 1600$) [48, 49]. These two biomarkers can be determined pre-operatively and have the utility of stratifying patients with resectable pancreatic cancer into distinct prognostic phenotypes after pancreatectomy. Patients with dual biomarker positivity are at significant risk of early recurrence, with almost half of these patients succumbing within 12 months after pancreatectomy (12-month survival rate = 54%) [49]. Aberrant S100A2 and S100A4 expression correlated strongly to the poor prognostic squamous subtype [4–6, 49]. *S100A2* gene expression is used in all subtype classifiers of pancreatic cancer, as hypomethylation is a characteristic feature which leads to overexpression in the squamous subtype [4]. S100A4 expression is more complex as it is regulated by Wnt and TGF-beta signalling, and can also be expressed in the microenvironment

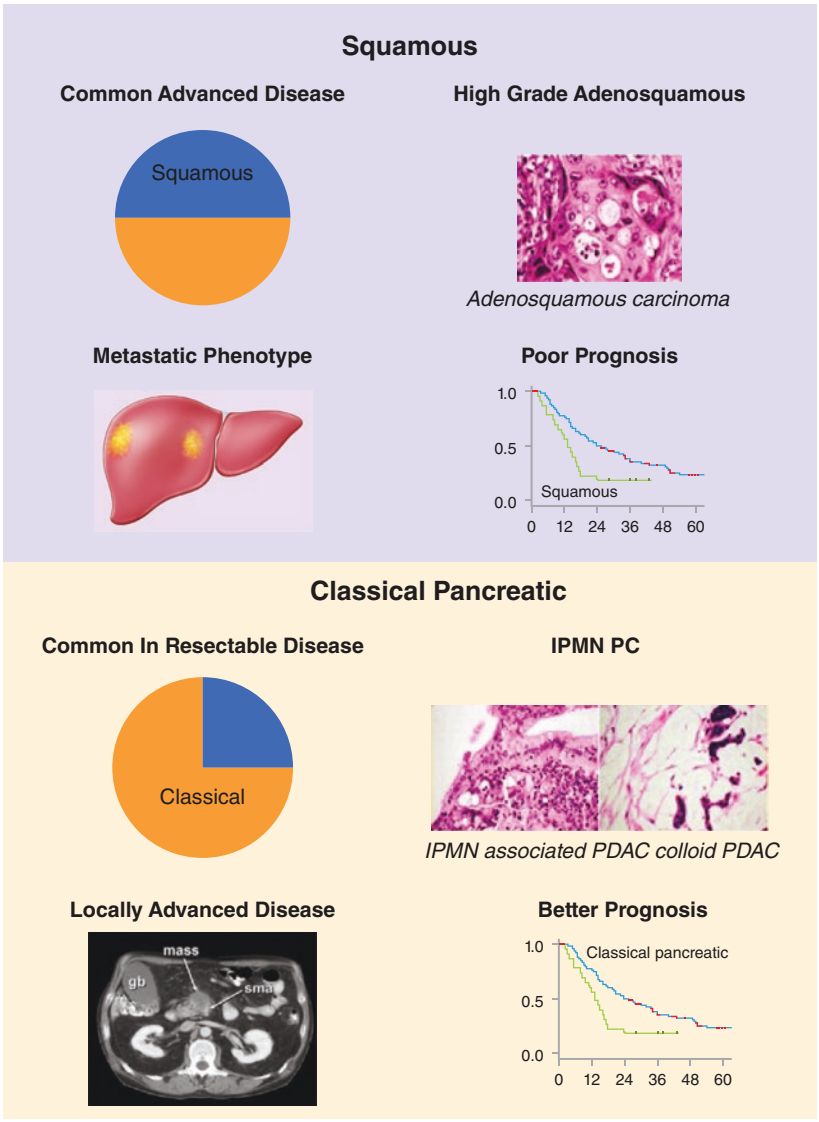

Fig. 21.4 Clinical and pathological disease patterns associated with molecular subtypes of pancreatic cancer. The ***squamous subtype*** is associated with advanced disease, metastatic phenotype, high pathological grade (poor differentiation) and adenosquamous differentiation. These are clinical features that have been associated and validated as poor prognostic markers of pancreatic cancer. The ***classical pancreatic subtype*** is associated with early stage disease and locally advanced pancreatic cancer in comparison to the squamous subtype. IPMN-associated pancreatic cancer is strongly associated with the classical pancreatic subtype and these features have been previously validated as predictors of better prognosis in pancreatic cancer. These molecular subtypes may underlie the differences in prognosis seen with these routine clinical and histological prognosticators

by lymphocytes and fibroblasts, which may be secondary to differential gene expression in the squamous subtype but requires further investigation [50]. These studies suggest that molecular subtyping, either by RNAseq or using candidate genes such as *S100A2*, can be used to better select patients for surgery. Avoiding surgery in an aggressive phenotype, whilst adopting aggressive surgical management in patients with more indolent disease (even in the setting of locally advanced pancreatic cancer), can hopefully improve the outcome following surgery for pancreatic cancer. Neoadjuvant therapy represents a paradigm change for pancreatic cancer, and how subtype and treatment response interact to determine outcome will be crucial to define the role of molecular subtyping in selecting patients for surgery in pancreatic cancer. These are questions being addressed in multiple international neoadjuvant trials in pancreatic cancer, including the PRIMUS 002 trial on the *PRECISION-Panc* platform [51–53].

21.6 Conclusions

Molecular subtyping has vastly changed our understanding of many cancer types, including pancreatic cancer. Contrasting molecular profiles are beginning to explain the clinical differences seen in histologically identical cancers. In the treatment of pancreatic cancer, particularly in the setting of surgical management and decision making, molecular subtyping has great potential to improve patient management. Now that we can accurately subtype patients before, during and after neoadjuvant therapy [53], the potential for utilising and adjusting to the plasticity of molecular lineages can be realised. This will allow for the era of precision surgery in pancreatic cancer to reach its full potential and improve the outcomes for patients following pancreatectomy.

References

1. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–11.
2. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
3. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019;16(4):207–20.
4. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47–52.
5. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med. 2011;17(4):500–3.
6. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47(10):1168–78.

7. Humphris JL, Patch AM, Nones K, Bailey PJ, Johns AL, McKay S, et al. Hypermutation in pancreatic cancer. Gastroenterology. 2017;152(1):68–74.e2.
8. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
9. Biankin AV, Maitra A. Subtyping pancreatic cancer. Cancer Cell. 2015;28(4):411–3.
10. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491(7424):399–405.
11. Hoadley KA, Yau C, Wolf DM, Cherniack AD, Tamborero D, Ng S, et al. Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell. 2014;158(4):929–44.
12. Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun. 2015;6:6744.
13. Hayashi A, Fan J, Chen R, Ho Y-j, Makohon-Moore AP, Lecomte N, et al. A unifying paradigm for transcriptional heterogeneity and squamous features in pancreatic ductal adenocarcinoma. Nat Cancer. 2020;1(1):59–74.
14. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
15. Fischer KR, Durrans A, Lee S, Sheng J, Li F, Wong ST, et al. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. Nature. 2015;527(7579):472–6.
16. Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature. 2015;527(7579):525–30.
17. Maurer C, Holmstrom SR, He J, Laise P, Su T, Ahmed A, et al. Experimental microdissection enables functional harmonisation of pancreatic cancer subtypes. Gut. 2019;68:953–4.
18. Candido JB, Morton JP, Bailey P, Campbell AD, Karim SA, Jamieson T, et al. CSF1R(+) macrophages sustain pancreatic tumor growth through T cell suppression and maintenance of key gene programs that define the squamous subtype. Cell Rep. 2018;23(5):1448–60.
19. Puleo F, Nicolle R, Blum Y, Cros J, Marisa L, Demetter P, et al. Stratification of pancreatic ductal adenocarcinomas based on tumor and microenvironment features. Gastroenterology. 2018;155(6):1999–2013.e3.
20. Zhang Y, Velez-Delgado A, Mathew E, Li D, Mendez FM, Flannagan K, et al. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut. 2017;66(1):124–36.
21. Jiang H, Hegde S, Knolhoff BL, Zhu Y, Herndon JM, Meyer MA, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat Med. 2016;22(8):851–60.
22. Xu Z, Vonlaufen A, Phillips PA, Fiala-Beer E, Zhang X, Yang L, et al. Role of pancreatic stellate cells in pancreatic cancer metastasis. Am J Pathol. 2010;177(5):2585–96.
23. Ikushima H, Miyazono K. TGFbeta signalling: a complex web in cancer progression. Nat Rev Cancer. 2010;10(6):415–24.
24. Martens S, Lefesvre P, Nicolle R, Biankin AV, Puleo F, Van Laethem JL, et al. Different shades of pancreatic ductal adenocarcinoma, different paths towards precision therapeutic applications. Ann Oncol. 2019;30(9):1428–36.
25. The Cancer Genome Atlas Research Network. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017;32(2):185–203.e13.
26. Noll EM, Eisen C, Stenzinger A, Espinet E, Muckenhuber A, Klein C, et al. CYP3A5 mediates basal and acquired therapy resistance in different subtypes of pancreatic ductal adenocarcinoma. Nat Med. 2016;22(3):278–87.
27. Knudsen ES, Balaji U, Mannakee B, Vail P, Eslinger C, Moxom C, et al. Pancreatic cancer cell lines as patient-derived avatars: genetic characterisation and functional utility. Gut. 2018;67(3):508–20.

28. Steele CW, Karim SA, Leach JD, Bailey P, Upstill-Goddard R, Rishi L, et al. CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell. 2016;29(6):832–45.
29. Kalimuthu SN, Wilson GW, Grant RC, Seto M, O'Kane G, Vajpeyi R, et al. Morphological classification of pancreatic ductal adenocarcinoma that predicts molecular subtypes and correlates with clinical outcome. Gut. 2020;69(2):317–28.
30. Aguirre AJ, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. Cancer Discov. 2018; https://doi.org/10.1158/2159-8290.CD-18-0275.
31. Karasinska JM, Topham JT, Kalloger SE, Jang GH, Denroche RE, Culibrk L, et al. Altered gene expression along the glycolysis-cholesterol synthesis axis is associated with outcome in pancreatic cancer. Clin Cancer Res. 2020;26(1):135–46.
32. Kuzu OF, Noory MA, Robertson GP. The role of cholesterol in cancer. Cancer Res. 2016;76(8):2063–70.
33. Baek G, Tse YF, Hu Z, Cox D, Buboltz N, McCue P, et al. MCT4 defines a glycolytic subtype of pancreatic cancer with poor prognosis and unique metabolic dependencies. Cell Rep. 2014;9(6):2233–49.
34. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metab. 2008;7(1):11–20.
35. Chan-Seng-Yue M, Kim JC, Wilson GW, Ng K, Figueroa EF, O'Kane GM, et al. Transcription phenotypes of pancreatic cancer are driven by genomic events during tumor evolution. Nat Genet. 2020;2(2):231–40.
36. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ, Australian Pancreatic Cancer Genome Initiative, et al. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br J Surg. 2018;105(2):e183–91.
37. Mackay TM, van Erning FN, van der Geest LGM, de Groot JWB, Haj Mohammad N, Lemmens VE, et al. Association between primary origin (head, body and tail) of metastasised pancreatic ductal adenocarcinoma and oncologic outcome: a population-based analysis. Eur J Cancer. 2018;106:99–105.
38. Artinyan A, Soriano PA, Prendergast C, Low T, Ellenhorn JD, Kim J. The anatomic location of pancreatic cancer is a prognostic factor for survival. HPB (Oxford). 2008;10(5):371–6.
39. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg. 2000;4(6):567–79.
40. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg. 1996;223(5):506–11; discussion 11–2.
41. Notta F, Chan-Seng-Yue M, Lemire M, Li Y, Wilson GW, Connor AA, et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. Nature. 2016;538(7625):378–82.
42. Jamal-Hanjani M, Wilson GA, McGranahan N, Birkbak NJ, Watkins TBK, Veeriah S, et al. Tracking the evolution of non-small-cell lung cancer. N Engl J Med. 2017;376(22):2109–21.
43. Birnbaum DJ, Finetti P, Birnbaum D, Mamessier E, Bertucci F. Validation and comparison of the molecular classifications of pancreatic carcinomas. Mol Cancer. 2017;16(1):168.
44. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
45. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg. 2004;240(2):293–8.
46. van Roessel S, Strijker M, Steyerberg EW, Groen JV, Mieog JS, Groot VP, et al. International validation and update of the Amsterdam model for prediction of survival after pancreatoduodenectomy for pancreatic cancer. Eur J Surg Oncol. 2020;46(5):796–803.
47. Strijker M, Chen JW, Mungroop TH, Jamieson NB, van Eijck CH, Steyerberg EW, et al. Systematic review of clinical prediction models for survival after surgery for resectable pancreatic cancer. Br J Surg. 2019;106(4):342–54.

48. Biankin AV, Kench JG, Colvin EK, Segara D, Scarlett CJ, Nguyen NQ, et al. Expression of S100A2 calcium-binding protein predicts response to pancreatectomy for pancreatic cancer. Gastroenterology. 2009;137(2):558–68. 68.e1–11.
49. Dreyer SB, Pinese M, Jamieson NB, Scarlett CJ, Colvin EK, Pajic M, et al. Precision oncology in surgery: patient selection for operable pancreatic cancer. Ann Surg. 2018; https://doi.org/10.1097/SLA.0000000000003143.
50. Fei F, Qu J, Zhang M, Li Y, Zhang S. S100A4 in cancer progression and metastasis: a systematic review. Oncotarget. 2017;8(42):73219–39.
51. Dreyer SB, Jamieson NB, Morton JP, Sansom OJ, Biankin AV, Chang DK. Pancreatic cancer: from genome discovery to PRECISION-Panc. Clin Oncol (R Coll Radiol). 2020;32(1):5–8.
52. Dreyer SB, Jamieson NB, Cooke SL, Valle JW, McKay CJ, Biankin AV, et al. PRECISION-Panc: the next generation therapeutic development platform for pancreatic cancer. Clin Oncol (R Coll Radiol). 2020;32(1):1–4.
53. Dreyer SB, Jamieson NB, Evers L, Duthie F, Cooke S, Marshall J, et al. Feasibility and clinical utility of endoscopic ultrasound guided biopsy of pancreatic cancer for next-generation molecular profiling. Chin Clin Oncol. 2019;8(2):16.

Chapter 22
The Role of Epigenetics in Pancreatic Ductal Adenocarcinoma

Marcus Roalsø, Øyvind Holsbø Hald, Daniel Ansari, Roland Andersson, and Kjetil Søreide

Take Home Messages

- Epigenetic changes are heritable DNA modifications affecting gene expression that do not involve changes in the nucleotide sequence of DNA.
- Epigenetic deregulation occurs early in tumor development, providing a potential for advancements in diagnostics and prognostication.
- Clinically relevant molecular subtypes of PDAC are composed of distinct epigenetic landscapes.
- Epigenetic alterations are potentially reversible and can therefore serve as targets for novel anti-cancer therapies.

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Pearls and Pitfalls
- The field of cancer epigenetics is emerging and not yet fully understood, but knowledge in this field is rapidly increasing.
- No proven epigenetic treatment options are currently available in pancreatic ductal adenocarcinoma, but several epigenetic modifying drugs are being evaluated in clinical trials.

Future Perspectives
- A more comprehensive understanding of the epigenetic changes present in pancreatic cancers can lead to novel therapies.
- Future epigenetic therapies may prove synergistic with existing therapeutic options.
- Liquid biopsy technology with analyses of epigenetic markers has potential as pre-diagnostic screening tools for patients with PDAC.
- The epigenome is altered throughout life due to various external factors suggesting preventive measures can be identified.

22.1 Introduction

Epigenetic alterations have been associated with cancer for over four decades, but only recently has the potential for clinical use in classification, as biomarkers or as targets for novel therapies been realized [1, 2]. Furthermore, epigenetic changes are now increasingly appreciated as essential for driving the cancer phenotype, including in pancreatic ductal adenocarcinoma (PDAC) [3–5]. The epigenetic regulation of cancer is complex and not yet fully understood, but application of epigenetics to clinical practice and in cancer research has the potential to improve cancer care.

This chapter will give a brief introduction to epigenetics as it is currently understood in general and in relation to pancreatic cancer development and its mechanisms. Also, epigenetics will be described in relation to the ability for diagnosis, prognosis or therapy for patients with pancreatic cancer.

22.2 General Aspects of Epigenetics

Epigenetic regulation is crucial in normal physiology and underpins how the cell- and tissue-specific transcriptomes of the human body can arise from an invariable genome. Epigenetic alterations (Box 22.1) are found across many solid organ cancers and are increasingly making clinical impact onto cancer management [4]. Novel epigenetic modifying drugs may be used for a more tailored and specific treatment of cancers. However, the interaction between the genome and epigenome throughout the process of carcinogenesis is not fully understood [6]. Epigenetic reprograming of neoplastic cells has been proposed, with the idea that the epigenome and genome present in tumor cells interact synergistically to evolve to stressors to ensure survival [7, 8].

Box 22.1 Epigenetic Alterations
Epigenetics refers to heritable changes in gene expression patterns that are not due to changes in the genetic code (primary DNA sequence), but rather occur through methylation of DNA, by histone modifications, and, through changes to chromatin structure to alter genetic expression. Each of the epigenetic levels can be influenced through inherited genetic information, through external exposures and ongoing biological processes, such as aging. Most importantly, epigenetic changes may lead to cancer development.

Box 22.2 Writers, Readers, and Erasers
- *Writers*: regulators that write the marks. Enzymes that catalyze the addition of specific posttranslational modifications onto DNA or histones. These include DNA methyltransferases, histone methyltransferases, and histone acetyltransferases.
- *Readers*: regulators that read the marks; protein or protein domains that are recruited to specific epigenetic marks to recognize and bind the mark. Reader domains may be present in writer and eraser enzymes or scaffolds that recruit additional effector proteins. These include regulators such as the bromodomain, chromodomain, and Tudor proteins.
- *Erasers*: regulators that can erase marks. Enzymes that catalyze the removal of a specific posttranslational modification from DNA or histones. These include histone deacetylases (HDAC) and histone demethylases (HDM) and remodelers of the chromatin, such as components of the SWI/SNF (SWItch/Sucrose Non-Fermentable) nucleosome remodelling complex.

22.2.1 Epigenetic Regulators

Several classes of epigenetic regulators exist and they are broadly defined as ‘writers’, ‘readers’ and ‘erasers’ [9, 10] (Box 22.2). As epigenetic alterations are reversible, inhibitors targeting the epigenetic processes may be promising anticancer strategies.

Mutation of specific epigenetic modifiers occurs frequently in a variety of cancers demonstrating that altered epigenetic regulation may play an important role in cancer development, yet may also be a bystander effect of carcinogenesis itself [11]. In general, the most explored epigenetic alteration is DNA methylation [12, 13].

22.2.2 Technical Platforms for Epigenetic Mapping

Technological advances in genome wide sequencing approaches addressing epigenetic modifications has greatly increased our understanding of the epigenome of both normal and malignant cells (some of the most central methods are summarized in Box 22.3) [14].

Box 22.3 Platforms for Genome-Wide Epigenetic Mapping

Whole genome bisulfite sequencing (WGBS): Bisulfite treatment of DNA converts unmethylated cytosine residues to uracil, whereas methylated cytosine (5-methylcytosine) is unaffected. Subsequent whole genome sequencing of bisulfite treated DNA can reveal the cytosine methylation status at single nucleotide resolution.

Chromatin immunoprecipitation sequencing (ChIP seq): Protein-DNA interactions are commonly studied by ChIP. ChIP utilizes antibodies specific for DNA-binding proteins to immunoprecipitate complexes of DNA-binding proteins bound to specific DNA sequences. The DNA sequences precipitating with the protein can then be subjected to whole genome sequencing thereby providing genome wide information of which genetic material the protein binds. With regards to epigenetics, antibodies to specific for various histone modifications are typically used.

Assay for Transposase-Accessible Chromatin sequencing (ATAC seq): ATAC makes use of a hyperactive Tn5 transposase, which inserts adapter sequences into regions of open chromatin. Subsequent whole genome sequencing can therefore reveal DNA regions of increased accessibility.

22.2.3 Life-Time Exposure to Nutrients, Toxins and Behavioral Traits

The human epigenome is influenced from cradle to grave (Fig. 22.1), with internal and external lifetime exposure influencing the epigenetic marks that may act as modifiers or drivers of carcinogenesis.

Exposures, including physical activity, nutrition, vitamins and medications, influence epigenetic regulation [15–18]. Some changes play an important role in the establishment and regulation of gene programs, but others seem to occur without any apparent known physiological role. Age-dependent loss of global methylation, together with hypermethylation of CpG islands associated with cancer-related genes, may be influenced by nutritional and metabolic factors [19]. Folate metabolism is known to modify epigenetic mechanisms under experimental conditions, and more recent findings have explored the important roles of vitamin C and D in maintenance of the epigenome [20, 21].

22.2.4 Epigenetics and the Hallmarks of Cancer

Epigenetic regulation is implicated in all the so-called hallmarks of cancer and altered chromatin states can result in activation of oncogenes and silencing of tumor suppressor genes leading to increased proliferation, evasion of growth suppression and cell death resistance [22] (Fig. 22.2).

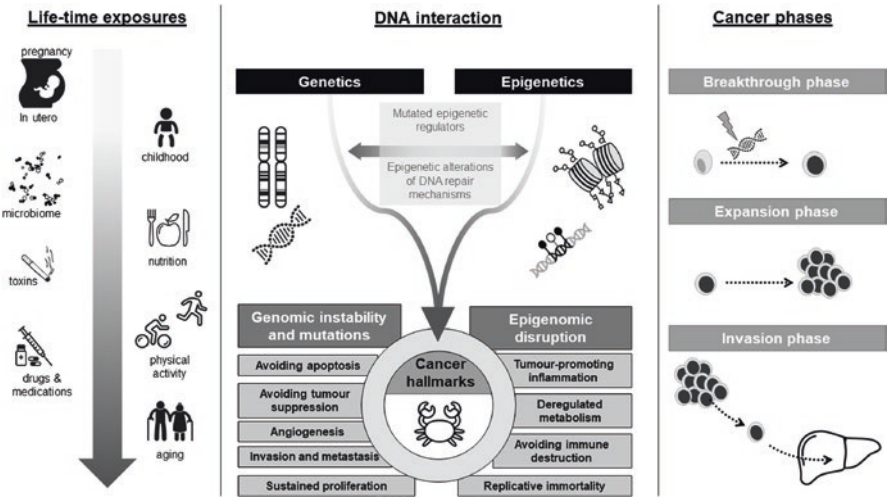

Fig. 22.1 Epigenetic changes, DNA interactions and cancer development. Epigenetic alterations occur throughout life. This influences the known hallmarks of cancer. Current research seeks to explore the exact mechanisms contributing to the different phases of malignant disease. (Reproduced from Drake TM, Soreide K. Cancer epigenetics in solid organ tumours: A primer for surgical oncologists. Eur J Surg Oncol. 2019;45(5):736–46, with permission from Elsevier)

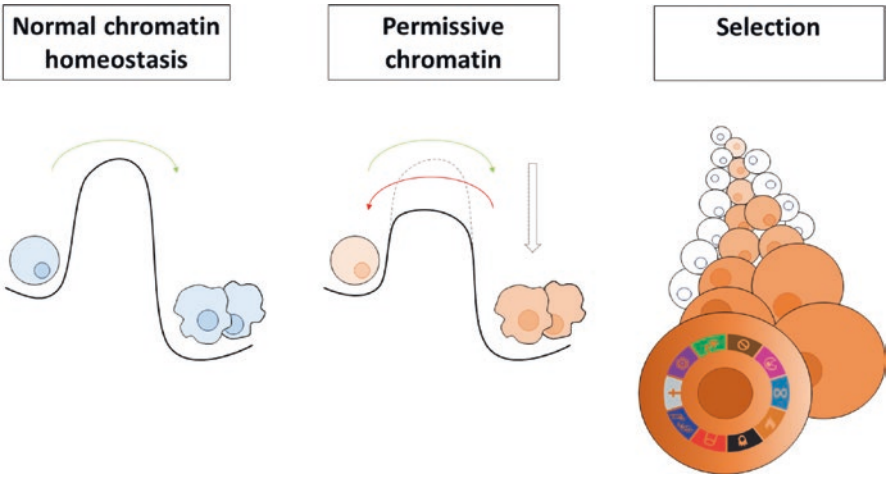

Fig. 22.2 Epigenetic regulation in tumor progression. Normal chromatin states (left) are essential for physiological gene expression and normal cellular homeostasis. Environmental, genetic, or metabolic factors can lead to the disruption of normal chromatin and induce pathologically permissive states resulting in epigenetic plasticity (middle). Epigenetic plasticity allows for the activation of gene regulatory programs promoting carcinogenesis and tumor progression (right). (Recreated from Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Science (New York, NY). 2017;357(6348))

22.2.5 Epigenetic Mechanisms in Carcinogenesis

Epigenetic alterations occur in concert with genetic mutations to influence the processes that drive the cancer phenotype in PDAC [23–25]. Notably, malignant tumors evolve in three broad phases—the *breakthrough*, *expansion* and *invasive* phases [26] (Fig. 22.1). In the breakthrough phase, a cell acquires a driver-gene mutation and begins to proliferate abnormally [26]. Known cancer mutation rates suggest that further mutations are unlikely to occur without a large increase in cell number during the breakthrough phase [27]. The mutation initiating the breakthrough phase is often very specific since a limited number of growth-regulating pathways seem able to initiate neoplasia in a given cell type [28]. As tumors progress, this specificity seems to be progressively lost, and a greater number of driver genes can further transform a cell in the expansion phase to the invasive phase. The fact that only a few somatic mutations are required for neoplastic transformation could possibly be explained by the added influence of epigenetic alterations [27].

22.3 Epigenetics in Pancreatic Ductal Adenocarcinoma

Alterations in epigenetic regulation are frequently found in PDAC [29–35], particularly in the regulation of genes involved with oncogenic signaling, with metabolic alterations [34, 36–39] and, in the metastatic process [40–43].

22.3.1 Epigenetics and the Development of PDAC

Cancers are largely considered to develop in a multifactorial stepwise manner through the accumulation of genetic and epigenetic aberrations. Pancreatic ductal adenocarcinoma initially progresses slowly and metastasize late during the genetic evolution [44]. Nevertheless, efforts in early detection of sporadic pancreatic cancer has seemingly not improved outcomes, and resectable tumors are increasingly treated using systemic therapies [45, 46]. The propensity for rapid metastasis seen after diagnosis counters the view of gradual progression. By tracking changes in DNA copy number and the associated rearrangements, the clonal evolution has been found consistent with a punctuated equilibrium model [47]. This model dictates that many of the genetic alterations in tumorigenesis appear over a short time interspersed by periods of stasis.

Deep whole-genome sequencing has shown that variations in chromosomal structures is an important factor of DNA damage in pancreatic carcinogenesis, in part due to inactivation of chromatin modifiers [48]. This suggests epigenetic alterations are at play in tumor progression. Indeed, primary human PDAC cells which had been reprogrammed with episomal vectors to reset their epigenetic profile demonstrated decreased tumorigenicity in vitro and in vivo [49].

22.3.2 Epigenetics and the Metastatic Process in PDAC

During the progression of PDAC, heterogeneous subclonal populations emerge that drive primary tumor growth, spread, distant metastasis, and eventually cause terminal illness. However, the genetic landscapes of metastases largely reflects that of the primary tumor in untreated patients, and PDAC driver mutations are shared by all subclones [39, 50]. This raises the possibility that an epigenetic process might operate to facilitate metastasis.

Based on a comprehensive analyses of comparative genomic analyses of primary tumors and metastases within individuals with pancreatic cancer, McDonald and colleagues suggested a model whereby linked metabolic-epigenetic programs are selected for enhanced tumorigenic fitness during the evolution of distant metastasis [39]. Their main discovery was that large-scale losses of heterochromatin marks, such as histone H3K9 and H4K20 methylation, and DNA methylation was associated with metastatic progression [41]. Unlike the uniform driver mutations that were seen across individual metastatic lesions, heterochromatin losses tended to occur in distant (for example, liver and lung) but not local (for example, peritoneal) PDAC metastases. Moreover, a subpopulation of heterochromatin deficient cells could be identified in the primary tumor, raising the possibility that this epigenetic state might have been selected for during seeding of distant metastases (Fig. 22.3).

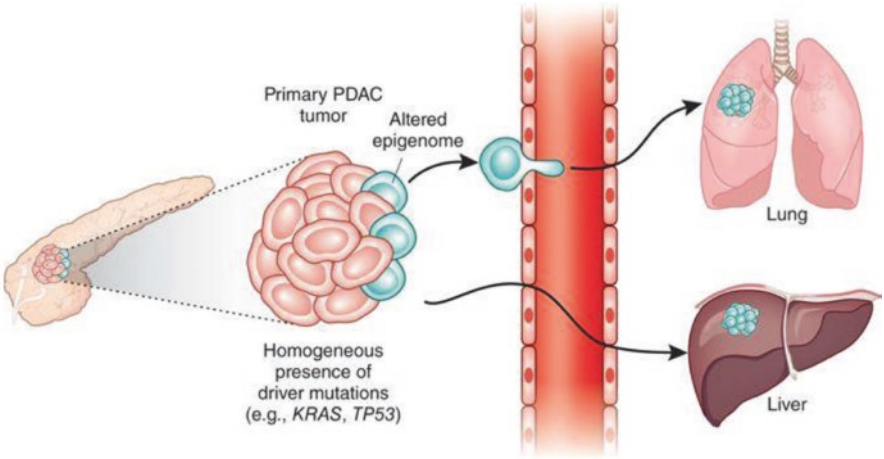

Fig. 22.3 An epigenomic reprogramming model of pancreatic cancer metastasis. Somatic driver mutations such as *KRAS* and *TP53* are usually present in all non-metastatic and metastatic subclones. At some timepoint an alteration of chromatin states emerges, likely causing the ability of cancer cells to form distant metastases resulting in widespread disease. (Reproduced from from Vakoc CR, Tuveson DA. Untangling the genetics from the epigenetics in pancreatic cancer metastasis. Nat Genet. 2017;49(3):323–4, with permission from Springer Nature)

22.3.3 Epigenetics and the Molecular Subtypes of PDAC

PDAC is currently classified into several subgroups, ranging from three to five subtypes [51, 52]. Transcriptome profiling has revealed two major molecular subtypes of pancreatic cancer, namely classical and basal [31] (Fig. 22.4). Classical tumors have a far better prognosis compared with basal subtypes with approximately four-fold longer median overall survival, underscoring the clinical relevance of the two subtypes [51].

Characterization of the mutational landscape of pancreatic cancer has provided limited clinically valuable information with regards to classifying the major molecular subtypes of pancreatic cancer, and there is emerging evidence that epigenetic changes underlie the different phenotypes [29]. Lomberk et al. studied the epigenomic landscape of PDAC subtypes grown as patient derived xenografts (PDX) using an integrative approach with ChIP sequencing (seq) on multiple histone marks, transcriptomic profiling (RNA seq) and genome wide methylation analysis. Basal subtypes were shown to have altered methylation of effectors and inhibitors of WNT signaling pathways, whereas classical tumors had hypomethylation and subsequent overexpression of cholesterol transporter NPC1L1. Furthermore, basal tumors were found to have deregulation of genes related to canonical oncogenic signaling networks, including the MYC, ErbB/EGFR, WNT, PI3K-AKT and TGFβ pathways. In addition, basal and classical tumors, were found to be composed of

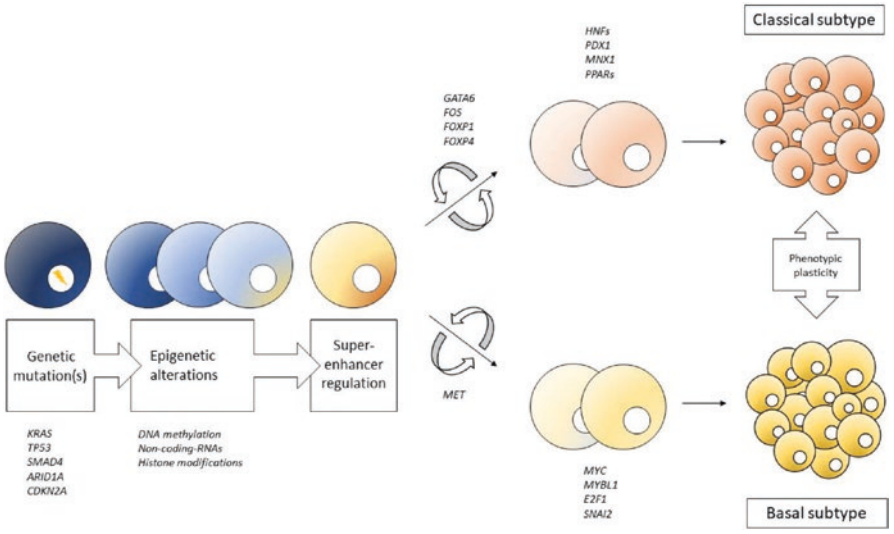

Fig. 22.4 Model detailing development of PDAC subtypes. Primary tumors are driven by a set of largely known mutations. These trigger epigenetic changes via various mechanisms, and distinct epigenetic alterations underlie the molecular subtypes of PDAC. (Recreated from Juiz NA, Iovanna J, Dusetti N. Pancreatic Cancer Heterogeneity Can Be Explained Beyond the Genome. Front Oncol. 2019;9:246, distributed under the terms of the Creative Commons Attribution License (CC BY))

distinct super enhancer states where super enhancers in classical tumors were associated with at least nine different transcription factors, while in basal tumors MET was associated with the regulation of basal-specific super enhancers. Interestingly, siRNA mediated knockdown of MET in PDX derived cell lines from basal tumors led to the conversion into the classical phenotype.

22.3.4 Epigenetic Mechanisms Shaping the Tumor Microenvironment

The last decade has seen a marked increase in research into the tumor microenvironment (TME), both with regards to the underlying biology and translational efforts [53, 54]. The TME is comprised of stromal and vascular structures, the extracellular matrix, together with infiltrating immune cells. The reciprocal interaction between malignant and non-cancer cells within the tumor impact carcinogenesis and tumor progression, while simultaneously mediating therapeutic resistance.

Changes in gene expression patterns driven by epigenetic changes occur both by direct contact between cells and through various secreted factors. Cancer-associated fibroblasts (CAFs) have been found to be altered by PDAC cells [55]. PDAC cell induced DNA methylation of the *SOCS1* gene in CAFs, a suppressor of pro-cancerous cytokines and growth factors, leading to increased growth of pancreatic tumor cells in vitro [56]. Further, clinical data showed an overall survival of more than 3 years in patients with CAFs lacking *SOCS1* methylation.

22.4 Epigenetics and the Role of Novel Therapies in PDAC

Over the last several years, a new generation of drugs directed at epigenetic modulators have entered clinical development, and results from these trials are now being disclosed. Various strategies are employed (Fig. 22.5). Unlike first-generation epigenetic therapies, newer agents are selective, and many are targeted to proteins which are mutated or translocated in cancer [57]. Several compounds have been investigated, targeted to epigenetic alterations in tumors, including trials of curcumin (a p300 histone acetyltransferase inhibitor) and histone deacetylase (HDAC) inhibitors such as Vorinostat [58]. Some patients have demonstrated a favorable response to these therapies, but more research is required to draw meaningful conclusions.

Epigenetic therapies alter several immuno-oncological mechanisms. Transposable elements such as neoantigens from retroviruses and previously restricted cancer antigens are reactivated. These are presented to immune cells in a ‘viral mimicry’ state, possibly inducing a favorable anti-tumor innate immune responses [59]. Both DNA methyltransferase (DNMT) and HDAC inhibitors transcriptionally upregulate factors such as tumor antigens, MHC class 1 and PD-1 ligands, all of which are important in tumor immunity (Fig. 22.6) [57].

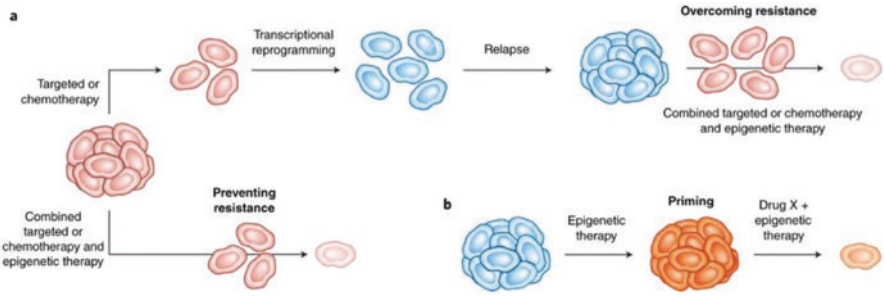

Fig. 22.5 Epigenetic treatment strategies. (**a**) Therapies targeting epigenetic modifiers can be utilized to prevent or overcome resistance to cytotoxic drugs, or (**b**) alter the transcriptional profile priming malignant cells increasing the efficacy of subsequent drug regimens. (Reproduced from Mohammad HP, Barbash O, Creasy CL. Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Nature medicine. 2019 Mar;25(3):403–18, with permission from Springer Nature)

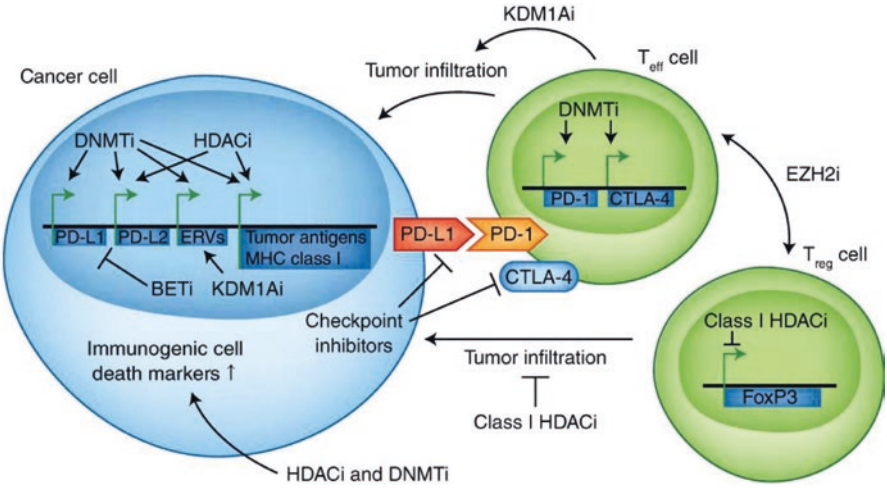

Fig. 22.6 Epigenetic therapies and tumor immunity. Epigenetic inhibitors (HDACi, DNMTi, KDMAi) upregulate several factors that are key players in antitumor immunity in both cancerous cells and tumor infiltrating leukocytes, such as tumor antigens, MHC class 1, and checkpoint inhibitors and their ligands. Further they induce hallmarks of immunogenetic cell death. (Reproduced from Mohammad HP, Barbash O, Creasy CL. Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Nature medicine. 2019 Mar;25(3):403–18, with permission from Springer Nature)

Epigenetic therapies seek to induce transcriptional changes, a response that takes several days to mediate. Monotherapy may not be efficacious, and combination therapies are therefore more likely to provide synergistical effects, combined with either standard chemotherapeutic care or newer targeted or immune-based therapies. For instance, DNMT inhibitors upregulate checkpoint proteins such as PD-1

and CTLA-4 in effector T cells, which contributes to immune exhaustion [60–62]. Concomitant checkpoint inhibitors may therefore cause increased efficacy increasing the antitumor response. Several trials registered in the ClinicalTrials.gov database are ongoing or planned (Table 22.1). A detailed overview of ongoing research, trials and mechanisms is provided elsewhere [58].

Table 22.1 List of trials with epigenetic targets in PDAC

Drug(s)	Combination agent(s)	Phase of study	Status	NCT number
Romidepsin Azacitidine	nab-Paclitaxel Gemcitabine Durvalumab Lenalidomide	Phase 1/2	Not yet recruiting	NCT04257448
Entinostat Molibresib		Phase 1	Not yet recruiting	NCT03925428
Entinostat	FOLFOX regimen	Phase 1	Not yet recruiting	NCT03760614
Azacitidine		Phase 2	Recruiting	NCT01845805
Entinostat	Nivolumab	Phase 2	Recruiting	NCT03250273
Vorinostat	Gemcitabine Sorafenib	Phase 1	Recruiting	NCT02349867
Panobinostat Vorinostat	Various +++	Phase 1	Recruiting	NCT03878524
Decitabine	Tetrahydrouridine	Phase 1	Completed	NCT02847000
Entinostat		Phase 1	Completed	NCT00020579
Vorinostat	Capecitabine	Phase 1	Completed	NCT00983268
Azacitidine	nab-Paclitaxel Carboplatin	Phase 1	Completed	NCT01478685
Vorinostat	NPI-0052 (marizomib)	Phase 1	Completed	NCT00667082
Panobinostat	Bortezomib	Phase 2	Terminated (Funding not available)	NCT01056601
Vorinostat		Phase 1/2	Terminated (Slow accrual)	NCT00831493
Vorinostat	5-FU	Phase 1/2	Terminated (Funding withdrawn)	NCT00948688
Azatacidine	Gemcitabine	Phase 1	Terminated (Miscellaneous reasons)	NCT01167816
Epigenetic targets				
Azacitidine Decitabane	Hypomethylates DNA by inhibition of DNA methyltransferase, halting cell division.			
Molibresib	Molibresib is a bromodomain and extra-terminal motif (BET) inhibitor, downregulating transcription of oncogenes.			
Vorinostat Entinostat Panobinostat Romidepsin	Histone deacetylase inhibitors induce growth arrest, differentiation, autophagy, and apoptosis in tumor cells.			

22.5 Epigenetics and Biomarkers for Early Detection of PDAC

Epigenetic alterations in pancreatic cancer offers a minimally invasive approach to diagnostics and prognostication [33, 35]. Cell-free DNA can easily be collected from bodily fluids, however more invasive procedures, such as harvesting pancreatic juices via endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS), all enable assessment of tumor cell DNA methylation.

Panels of epigenetic biomarkers have demonstrated to achieve sensitivities and specificities of 80–90%, but lack external validation and have not entered routine clinical practice [63, 64]. However, recent panels have shown promise for liquid biopsy technology as a pre-diagnostic screening tool for patients with PDAC. One approach is the analysis of circulating nucleosomes, which are sections of DNA wrapped around a histone core, which are released into the circulation. Since epigenetic changes occur early in tumorigenesis, analyzing tumor derived nucleosomes can provide a viable screening option. However, identifying epigenetic profiles discriminating malignant from benign disease has been troublesome. Nonetheless, nucleosomes have been found to distinguish pancreatic cancer from healthy controls [65]. A test by Bauden et al. has an area under the curve (AUC) of 0.95, which is superior to the only FDA approved biomarker for pancreatic cancer, CA 19-9, which has an AUC of 0.87. Combining the two exhibits an AUC of 0.98, with an overall sensitivity of 92% and specificity of 90%.

22.6 Conclusion

Epigenetic alterations are important in PDAC. Exposures accumulated over a lifetime likely modulate tumorigenesis and the risk and evolution of metastatic disease. Epigenetic markers are currently being explored for use as early biomarkers detecting subclinical disease. Epigenetics may further be specific to subtypes of PDAC and thus have potential for therapeutic intervention, currently of which several are in the pipeline (Fig. 22.7). As the understanding of epigenetics progresses, it may yield novel ways of understanding and treating PDAC.

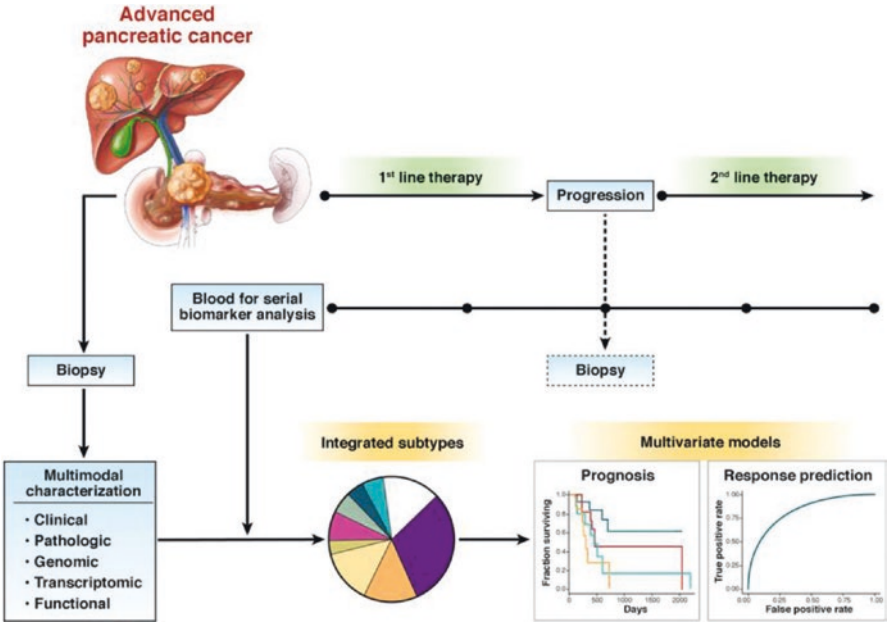

Fig. 22.7 Multimodal characterization of PDAC. Multimodal characterization of pancreatic tumors reveals various subtypes, which can direct treatment options and help in prognostication

References

1. Rodriguez-Paredes M, Esteller M. Cancer epigenetics reaches mainstream oncology. Nat Med. 2011;17(3):330–9.
2. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. Cell. 2012;150(1):12–27.
3. Trager MM, Dhayat SA. Epigenetics of epithelial-to-mesenchymal transition in pancreatic carcinoma. Int J Cancer. 2017;141(1):24–32.
4. Drake TM, Soreide K. Cancer epigenetics in solid organ tumours: a primer for surgical oncologists. Eur J Surg Oncol. 2019;45(5):736–46.
5. Natale F, Vivo M, Falco G, Angrisano T. Deciphering DNA methylation signatures of pancreatic cancer and pancreatitis. Clin Epigenetics. 2019;11(1):132.
6. Shen H, Laird PW. Interplay between the cancer genome and epigenome. Cell. 2013;153(1):38–55.
7. Suva ML, Riggi N, Bernstein BE. Epigenetic reprogramming in cancer. Science. 2013;339(6127):1567–70.
8. Chatterjee A, Rodger EJ, Eccles MR. Epigenetic drivers of tumourigenesis and cancer metastasis. Semin Cancer Biol. 2018;51:149–59.
9. Esteve-Puig R, Bueno-Costa A, Esteller M. Writers, readers and erasers of RNA modifications in cancer. Cancer Lett. 2020;474:127–37.
10. Biswas S, Rao CM. Epigenetic tools (The Writers, The Readers and The Erasers) and their implications in cancer therapy. Eur J Pharmacol. 2018;837:8–24.
11. Nebbioso A, Tambaro FP, Dell'Aversana C, Altucci L. Cancer epigenetics: moving forward. PLoS Genet. 2018;14(6):e1007362.

12. Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358(11):1148–59.
13. Dor Y, Cedar H. Principles of DNA methylation and their implications for biology and medicine. Lancet. 2018;392(10149):777–86.
14. Kagohara LT, Stein-O'Brien GL, Kelley D, Flam E, Wick HC, Danilova LV, et al. Epigenetic regulation of gene expression in cancer: techniques, resources and analysis. Brief Funct Genomics. 2018;17(1):49–63.
15. Etchegaray JP, Mostoslavsky R. Interplay between metabolism and epigenetics: a nuclear adaptation to environmental changes. Mol Cell. 2016;62(5):695–711.
16. Daniel M, Tollefsbol TO. Epigenetic linkage of aging, cancer and nutrition. J Exp Biol. 2015;218(Pt 1):59–70.
17. Johnson IT, Belshaw NJ. The effect of diet on the intestinal epigenome. Epigenomics. 2014;6(2):239–51.
18. Nasir A, Bullo MMH, Ahmed Z, Imtiaz A, Yaqoob E, Jadoon M, et al. Nutrigenomics: epigenetics and cancer prevention: a comprehensive review. Crit Rev Food Sci Nutr. 2020;60(8):1375–87.
19. Boukouris AE, Zervopoulos SD, Michelakis ED. Metabolic enzymes moonlighting in the nucleus: metabolic regulation of gene transcription. Trends Biochem Sci. 2016;41(8):712–30.
20. Camarena V, Wang G. The epigenetic role of vitamin C in health and disease. Cell Mol Life Sci. 2016;73(8):1645–58.
21. Fetahu IS, Hobaus J, Kallay E. Vitamin D and the epigenome. Front Physiol. 2014;5:164.
22. Flavahan WA, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. Science. 2017;357(6348):eaal2380.
23. Gonzalez-Borja I, Viudez A, Goni S, Santamaria E, Carrasco-Garcia E, Perez-Sanz J, et al. Omics approaches in pancreatic adenocarcinoma. Cancers. 2019;11(8):1052.
24. Kong L, Liu P, Zheng M, Xue B, Liang K, Tan X. Multi-omics analysis based on integrated genomics, epigenomics and transcriptomics in pancreatic cancer. Epigenomics. 2020;12:507–24.
25. Mishra NK, Southekal S, Guda C. Survival analysis of multi-omics data identifies potential prognostic markers of pancreatic ductal adenocarcinoma. Front Genet. 2019;10:624.
26. Vogelstein B, Kinzler KW. The path to cancer—three strikes and you're out. N Engl J Med. 2015;373(20):1895–8.
27. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013;339(6127):1546–58.
28. Gerlinger M, Rowan A, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–92.
29. Lomberk G, Blum Y, Nicolle R, Nair A, Gaonkar KS, Marisa L, et al. Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes. Nat Commun. 2018;9(1):1978.
30. Dandawate P, Ghosh C, Palaniyandi K, Paul S, Rawal S, Pradhan R, et al. The histone demethylase KDM3A, increased in human pancreatic tumors, regulates expression of DCLK1 and promotes tumorigenesis in mice. Gastroenterology. 2019;157(6):1646–59.e11.
31. Juiz NA, Iovanna J, Dusetti N. Pancreatic Cancer heterogeneity can be explained beyond the genome. Front Oncol. 2019;9:246.
32. Sato N, Matsubayashi H, Abe T, Fukushima N, Goggins M. Epigenetic down-regulation of CDKN1C/p57KIP2 in pancreatic ductal neoplasms identified by gene expression profiling. Clin Cancer Res. 2005;11(13):4681–8.
33. Majumder S, Raimondo M, Taylor WR, Yab TC, Berger CK, Dukek BA, et al. Methylated DNA in pancreatic juice distinguishes patients with pancreatic cancer from controls. Clin Gastroenterol Hepatol. 2020;18(3):676–83.e3.
34. Ferrer J, Real FX. The cis-regulatory switchboard of pancreatic ductal cancer. EMBO J. 2016;35(6):558–60.
35. Kisiel JB, Raimondo M, Taylor WR, Yab TC, Mahoney DW, Sun Z, et al. New DNA methylation markers for pancreatic Cancer: discovery, tissue validation, and pilot testing in pancreatic juice. Clin Cancer Res. 2015;21(19):4473–81.

36. Soreide K, Sund M. Epidemiological-molecular evidence of metabolic reprogramming on proliferation, autophagy and cell signaling in pancreas cancer. Cancer Lett. 2015;356(2 Pt A):281–8.
37. Evan GI, Hah N, Littlewood TD, Sodir NM, Campos T, Downes M, et al. Re-engineering the pancreas tumor microenvironment: a "regenerative program" hacked. Clin Cancer Res. 2017;23(7):1647–55.
38. Koutsioumpa M, Hatziapostolou M, Polytarchou C, Tolosa EJ, Almada LL, Mahurkar-Joshi S, et al. Lysine methyltransferase 2D regulates pancreatic carcinogenesis through metabolic reprogramming. Gut. 2019;68(7):1271–86.
39. McDonald OG, Li X, Saunders T, Tryggvadottir R, Mentch SJ, Warmoes MO, et al. Epigenomic reprogramming during pancreatic cancer progression links anabolic glucose metabolism to distant metastasis. Nat Genet. 2017;49(3):367–76.
40. Roe JS, Hwang CI, Somerville TDD, Milazzo JP, Lee EJ, Da Silva B, et al. Enhancer reprogramming promotes pancreatic cancer metastasis. Cell. 2017;170(5):875–88.e20.
41. Vakoc CR, Tuveson DA. Untangling the genetics from the epigenetics in pancreatic cancer metastasis. Nat Genet. 2017;49(3):323–4.
42. Botla SK, Savant S, Jandaghi P, Bauer AS, Mucke O, Moskalev EA, et al. Early epigenetic downregulation of microRNA-192 expression promotes pancreatic cancer progression. Cancer Res. 2016;76(14):4149–59.
43. Mostoslavsky R, Bardeesy N. Reprogramming enhancers to drive metastasis. Cell. 2017;170(5):823–5.
44. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature. 2010;467(7319):1114–7.
45. Chari ST, Kelly K, Hollingsworth MA, Thayer SP, Ahlquist DA, Andersen DK, et al. Early detection of sporadic pancreatic cancer: summative review. Pancreas. 2015;44(5):693–712.
46. Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. J Natl Cancer Inst. 2014;106(3):dju011.
47. Notta F, Chan-Seng-Yue M, Lemire M, Li Y, Wilson GW, Connor AA, et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. Nature. 2016;538(7625):378–82.
48. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
49. Khoshchehreh R, Totonchi M, Carlos Ramirez J, Torres R, Baharvand H, Aicher A, et al. Epigenetic reprogramming of primary pancreatic cancer cells counteracts their in vivo tumourigenicity. Oncogene. 2019;38(34):6226–39.
50. Makohon-Moore AP, Zhang M, Reiter JG, Bozic I, Allen B, Kundu D, et al. Limited heterogeneity of known driver gene mutations among the metastases of individual patients with pancreatic cancer. Nat Genet. 2017;49(3):358–66.
51. Puleo F, Nicolle R, Blum Y, Cros J, Marisa L, Demetter P, et al. Stratification of pancreatic ductal adenocarcinomas based on tumor and microenvironment features. Gastroenterology. 2018;155(6):1999–2013.e3.
52. Martens S, Lefesvre P, Nicolle R, Biankin AV, Puleo F, Van Laethem JL, et al. Different shades of pancreatic ductal adenocarcinoma, different paths towards precision therapeutic applications. Ann Oncol. 2019;30(9):1428–36.
53. Neesse A, Algul H, Tuveson DA, Gress TM. Stromal biology and therapy in pancreatic cancer: a changing paradigm. Gut. 2015;64(9):1476–84.
54. Neesse A, Bauer CA, Ohlund D, Lauth M, Buchholz M, Michl P, et al. Stromal biology and therapy in pancreatic cancer: ready for clinical translation? Gut. 2019;68(1):159–71.
55. Garcia-Gomez A, Rodriguez-Ubreva J, Ballestar E. Epigenetic interplay between immune, stromal and cancer cells in the tumor microenvironment. Clin Immunol. 2018;196:64–71.
56. Xiao Q, Zhou D, Rucki AA, Williams J, Zhou J, Mo G, et al. Cancer-associated fibroblasts in pancreatic cancer are reprogrammed by tumor-induced alterations in genomic DNA methylation. Cancer Res. 2016;76(18):5395–404.

57. Mohammad HP, Barbash O, Creasy CL. Targeting epigenetic modifications in cancer therapy: erasing the roadmap to cancer. Nat Med. 2019;25(3):403–18.
58. Hessmann E, Johnsen SA, Siveke JT, Ellenrieder V. Epigenetic treatment of pancreatic cancer: is there a therapeutic perspective on the horizon? Gut. 2017;66(1):168–79.
59. Jones PA, Ohtani H, Chakravarthy A, De Carvalho DD. Epigenetic therapy in immune-oncology. Nat Rev Cancer. 2019;19(3):151–61.
60. Yang H, Bueso-Ramos C, DiNardo C, Estecio MR, Davanlou M, Geng QR, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia. 2014;28(6):1280–8.
61. Woods DM, Sodre AL, Villagra A, Sarnaik A, Sotomayor EM, Weber J. HDAC inhibition upregulates PD-1 ligands in melanoma and augments immunotherapy with PD-1 blockade. Cancer Immunol Res. 2015;3(12):1375–85.
62. Loo Yau H, Ettayebi I, De Carvalho DD. The cancer epigenome: exploiting its vulnerabilities for immunotherapy. Trends Cell Biol. 2019;29(1):31–43.
63. Firpo MA, Boucher KM, Mulvihill SJ. Prospects for developing an accurate diagnostic biomarker panel for low prevalence cancers. Theor Biol Med Model. 2014;11:1–9.
64. Syren P, Andersson R, Bauden M, Ansari D. Epigenetic alterations as biomarkers in pancreatic ductal adenocarcinoma. Scand J Gastroenterol. 2017;52(6–7):668–73.
65. Bauden M, Pamart D, Ansari D, Herzog M, Eccleston M, Micallef J, et al. Circulating nucleosomes as epigenetic biomarkers in pancreatic cancer. Clin Epigenetics. 2015;7:106.

Part V
Diagnosis, Imaging and Staging

Chapter 23
Early Diagnosis of Sporadic Pancreatic Cancer

Kjetil Søreide

Take Home Messages

- Screening for pancreatic cancer in asymptomatic, average-risk individuals is currently not recommended and should be avoided
- Several biomarkers have been proposed but none are currently in routine use for early diagnosis or screening
- Defining at-risk groups, such as new-onset diabetes in patients >50 years, may be useful to enrich at-risk populations for future cohort studies

Pearls and Pitfalls

- Hereditary or genetic syndromes represent the most prominent group for surveillance at the current time
- Screening in asymptomatic individuals is associated with high risk of false positive tests and risk of harms that outweighs benefits with available methods
- The promise of biomarkers and 'omics' technology has yet to make a major breakthrough in early cancer detection
- Several proposed biomarker studies lack external validation or, have shown considerably lower accuracy in external validation studies than in the original data
- Many studies suffer from biopsies or tissues being taken at time of diagnosis, hence invalidating the value of a time-dependent lag of the biomarker before a clinically detectable but asymptomatic cancer can be found

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Future Perspectives

- Investigating new technologies and 'omics' for early diagnosis will be essential, including image-based radiomics approaches, artificial intelligence and machine learning
- Novel biomarkers for early detection may stem from various body fluids ('liquid biopsies' from blood) or volatile compounds found in breath or urine tests
- Several novel technological platforms are explored for their ability to detect PDAC

23.1 Introduction

Most pancreatic cancers (some 80%) are diagnosed at a time when the patients already have symptoms, locally irresectable disease and/or metastasis. Currently, only 15–20% are diagnosed at a stage when curative surgery may be entertained. Symptoms are vague and unspecific for most patients. Patients with weight loss presenting to general practitioners in primary care may be a robust indicator for an underlying cancer to warrant referral and work up [1], but this is usually associated with an already advanced disease state (Fig. 23.1). Likewise, silent jaundice may be a diagnostic marker with need for work up, but usually present late and with advanced disease in most instances. Indeed, identifying robust, valid risk factors that would allow for appropriate screening for an early detection of PDAC has proven to be of some challenge, as demonstrated in several epidemiological models [2–5].

To be effective in screening preferably, the disease should be diagnosed at an early, asymptomatic stage when cure is possible, but this is a rare event in clinical practice [6]. Even in early stage cancers, only about one in five may present without any symptoms [7]. Unfortunately, there are no designated diagnostic or *screening tests* for pancreatic cancer. Indeed, pancreatic cancer does not suit the criteria and principles set out for justifying public screening programmes (Box 23.1) given the overall low incidence of disease and the current lack of accurate, inexpensive and non-invasive screening tests [8]. The consensus is that widespread population-based screening for pancreatic cancer in the general population or in patients with only one affected first-degree relative is neither practicable nor indicated in most countries [9, 10]. Indeed, the US Preventive Services Task Force concluded in a report that screening for pancreatic cancer would not improve disease-specific survival based on the rapid progression of the disease; the overall benefits was estimated to be small at best; and, that screening would be associated by a modest risk of harms [11, 12].

An ideal test for *early detection* (and, prevention) would include a sensitive, accurate serum marker to detect asymptomatic cancers that are clinically, and radiographically undetectable. Additionally, the marker should allow isolation of the

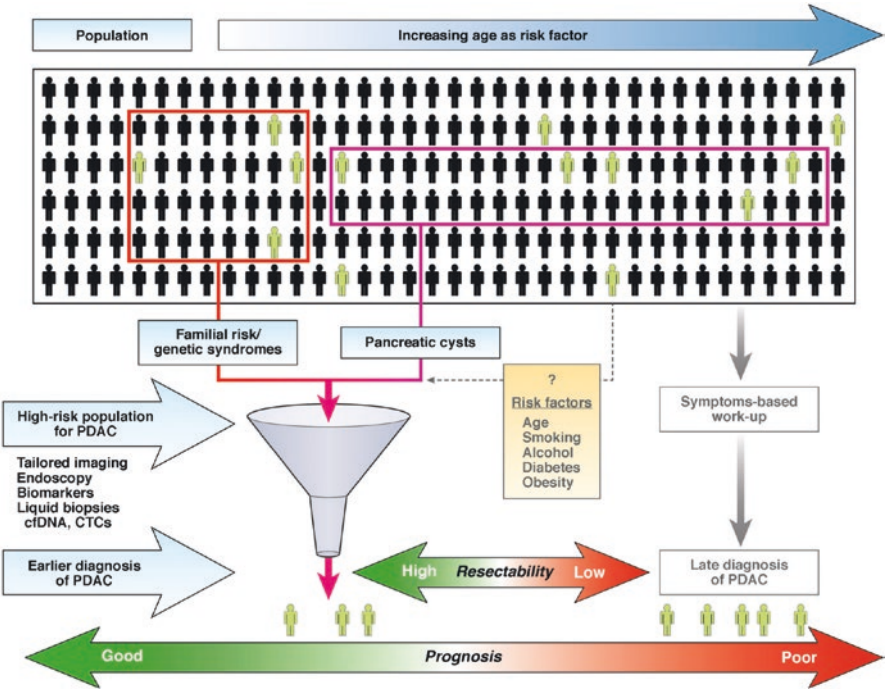

Fig. 23.1 Pancreatic cancer and challenges to early diagnosis in the population. Population-based screening of pancreatic cancer is made difficult by its relative low incidence. Risk populations are currently restricted to hereditary genetic syndromes and pancreatic cysts. Risk of pancreatic cancer increases with age, but otherwise the known risk factors are nonspecific (yellow box) and there is an unmet need for better risk features. An overall goal is to increase resectability by earlier diagnosis and thus prognosis. This goal can be facilitated by identification of novel high-risk groups that would be suitable targets for tailored surveillance. (Reproduced from Soreide K. Sweet Predictions Speak Volumes for Early Detection of Pancreatic Cancer. Gastroenterology 2018;155(2):265–268 with permission from Elsevier © 2018)

organ involved and, since the lesion is too small to detect be able to be treated with natural products to prevent growth and for the marker to become undetectable. The sensitivity of a biomarker-based screening test (Box 23.1; criterion 3) will need to be much higher for cancers with a modest public health burden than for those with larger burdens [13]. One important reason is that small changes in the sensitivity of any biomarker (or, a panel of biomarkers; or, any given imaging study) used for screening can have modest or enormous impacts on system-wide costs per cancer detected [14], depending on the prevalence of the disease being screened [15, 16].

A screening test that satisfies all these criteria (Box 23.1) is not available for pancreatic cancer. The early detection of asymptomatic, or at least early curable disease, remains an Achilles heel in pancreatic cancer. In this chapter we will discuss some aspects to the development in this field.

Box 23.1 Criteria for a Successful Screening Test

1. The disease should represent a substantial burden at the public health level and should have a prevalent, asymptomatic, non-metastatic phase.
2. The asymptomatic, non-metastatic phase should be recognizable.
3. The screening test should have reasonable sensitivity, specificity and predictive value, be of low risk and low cost, and be acceptable to both the screener and the person screened.
4. Curative potential should be substantially better in early compared with advanced stages of disease.
5. Treatment of patients whose disease is detected by screening should decrease cause-specific mortality.

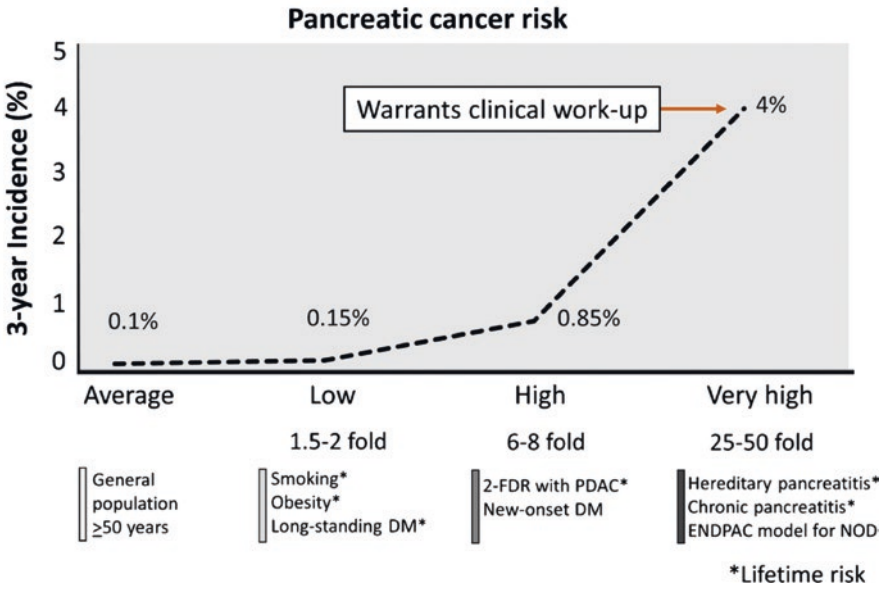

Fig. 23.2 Estimates of pancreatic cancer risk in populations. Schematic diagram showing incidence risk of pancreatic cancer in currently known risk groups. Compared to long-standing diabetes, new-onset diabetes has a significantly higher risk. This risk is further elevated with the clinical risk prediction model such as ENDPAC score. (Reproduced from Sharma A, Chari ST. Pancreatic Cancer and Diabetes Mellitus. Curr Treat Options Gastroenterol. 2018 Dec;16(4):466–478 with permission Springer © 2018)

23.2 Population at Risk

The majority of patients with pancreatic cancer are diagnosed after work-up based on symptoms (Fig. 23.1), with some higher-risk groups (e.g. familial risk or pancreatic cysts) undergoing surveillance [17, 18]. The most common risk factors—such as age, smoking, obesity—are generic and do not warrant screening per se (Fig. 23.2). Hence, most patients are unfortunately diagnosed late, at an advanced

Box 23.2 Principles of *Define*, *Enrich*, and *Find* Strategy for Early Detection of PDAC

- ***Define***, a high-risk population for PDAC (for example new-onset diabetes)
- ***Enrich***, a clinical risk model that can distinguish type-2 diabetes from PDAC-diabetes
- ***Find***, design prospective protocols for surveillance and/or intervention of cohorts

disease stage, when cure is no longer possible. The need to narrow the sieve (Fig. 23.1) through which subjects with a particular risk is enriched (Box 23.2), is of importance to increase accuracy and cost-effectiveness of screening for early detection.

In more recent trends reported from the USA an increasing proportion of patients are diagnosed with early stage cancers (stage IA) and with a slightly decreasing age for those diagnosed, suggesting that awareness and closer surveillance of high-risk groups may contribute to an earlier diagnosis [19]. Although this is a positive observation, the relative contribution is small, with <1% being diagnosed as "early cancers" in the beginning of the study period only to rise to <3% at the end. This is in parallel to a study from England, showing that stage I made up <1% of all resected pancreatic cancers, and stage II were <2% of all [20]. A similar rate was corroborated in a multi-center Japanese cohort, with <1% and 3% being stage I and II, respectively [7]. Hence, early-stage cancers make up but a miniscule share of pancreatic cancers at time of diagnosis. Also, a screening test would require a very high diagnostic specificity (>95%) to avoid generating too many false-positive tests [21].

One way of increasing the effectiveness of a screening approach would be to narrow down the population at-risk going through the screening system (the sieve; Fig. 23.1). This is done for certain populations with hereditary syndromes and familial pancreatic cancer (discussed in other chapters) [22]. Other at-risk groups include persons with pancreatic cystic lesions, for which some needs surveillance while other may need resection (see specific chapters in this book).

A specific risk group of recent attention is subjects >50 years of age with new-onset diabetes (Fig. 23.2)—a population with the highest risk for sporadic PDAC [23]. However, even in this scenario with an estimated pancreatic cancer prevalence of 0.8% the risk-benefit scenario is complex even with an assumed very sensitive and specific test (Box 23.3) [21].

While a difference in risk exists for long-standing to new onset diabetes, there has been an interest in blood glucose (or, fasting blood glucose) for a long time, as there is a strong correlation to risk of developing PDAC [24]. In one meta-analysis, with every 0.56 mmol/L increase in fasting blood glucose there was an associated with a 14% increase in the rate of PDAC [25]. In a model called ENPAC (Enriching New-Onset Diabetes for Pancreatic Cancer) based on changes in weight, change in blood glucose, and age at onset of diabetes, found subjects with a score ≥3 to have

Box 23.3 Challenges to a Clinically Useful Pancreatic Cancer Screening Test

If a hypothetical biomarker blood test was available with outstanding diagnostic characteristics (95% specificity when applied to its target population and 80% sensitivity for detecting stage I pancreatic cancer) and if it was applied to a population of 10,000 new-onset diabetics with an age >50 years*:

- 64 individuals with positive tests (***true positives***) could proceed with further diagnostic evaluation (e.g., pancreatic CT scan and pancreatic endoscopic ultrasound [EUS]) to diagnose their pancreatic cancer
- 16 would have a ***false-negative test*** (the pancreatic cancer would go undetected), and
- 500 would receive a ***false-positive test*** and have to undergo multiple additional tests before pancreatic cancer could be ruled out.

**estimated pancreatic cancer prevalence of 0.8%*

80% sensitivity and specificity for developing pancreatic cancer, but with need to perform external validation for the test [5]. However, such risk scores would improve risk-stratification that would further improve the diagnostic yield by use of a screening test or modality.

23.3 Conventional Imaging

Cross sectional imaging modalities are the reference standard at the moment for diagnosing lesions in the pancreas. These consist of endoscopic ultrasound (EUS), computed tomography (CT) and magnetic resonance imaging (MRI), and are discussed in detail elsewhere in this book. Suffice to say here, is that they each have benefits and disadvantages (Fig. 23.3), and all are equally accurate in diagnosing pancreatic cancer [26], together with transabdominal ultrasound and contrast-enhanced ultrasound [27]. Despite this, none of them are practical as stand-alone screening tools in regular-at-risk individuals.

23.3.1 Screening of High-Risk Individuals

Patients with high risk (>5% life-time risk) of PDAC are currently offered screening in certain programmes, it typically involves individuals with familial PDAC or heritable germline mutations (discussed elsewhere in this book). A systematic review [28] looked at prospective cohort studies (>20 patients) of asymptomatic adults determined to be at high-risk of pancreatic cancer (lifetime risk >5%, including specific

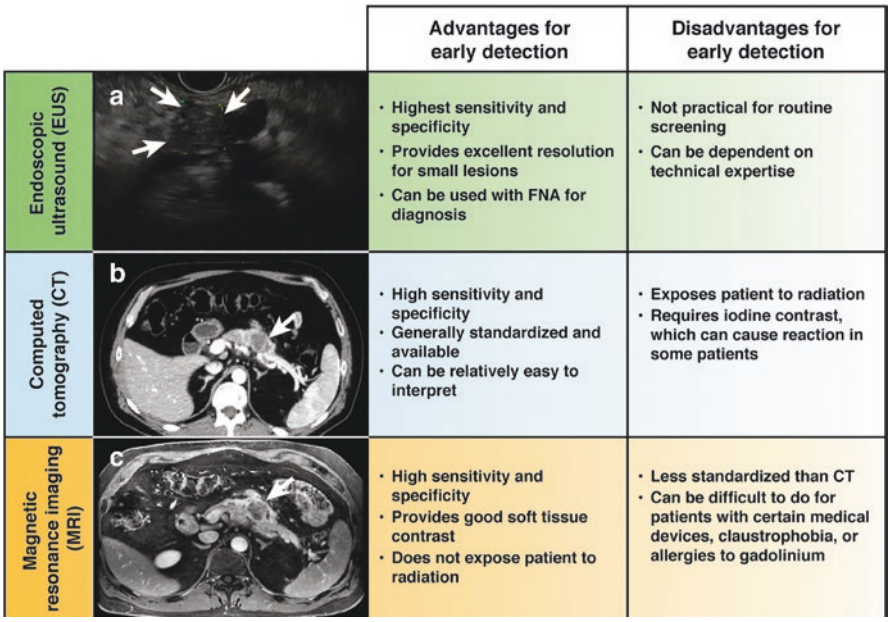

Fig. 23.3 Pearls and pitfalls in imaging for early detection of pancreatic cancer. Common imaging modalities for pancreatic cancer, including (A) EUS, (B) CT, and (C) MRI. Each image shows a patient with an approximately 2-cm lesion in the body of the pancreas. Each modality has advantages and disadvantages for the purposes of early detection of PDAC. A few practical considerations are enumerated. (Reproduced from Singhi AD, Koay EJ, Chari ST, Maitra A. Early Detection of Pancreatic Cancer: Opportunities and Challenges. Gastroenterology 2019;156(7):2024–2040 with permission from Elsevier)

genetic-associated conditions) who were screened by endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) to detect pancreatic lesions. The investigators [28] found 19 studies comprising 7085 individuals at high risk for pancreatic cancer. Of these, 1660 patients were evaluated by EUS and/or MRI. Fifty-nine high-risk lesions were identified (43 adenocarcinomas, of which 28 during the initial exam and 15 during follow-up surveillance) and 257 patients had pancreatic surgery. Based on the meta-analysis [28], the overall diagnostic yield screening for high risk pancreatic lesions was 0.74 (95% CI, 0.33–1.14), with moderate heterogeneity among studies. The 'number needed to screen' to identify one patient with a high-risk lesion was 135 (95% CI, 88–303). The diagnostic yield was similar for patients with different genetic features that increased risk, and whether patients were screened by EUS or MRI [28].

23.3.2 Visible Precursor Lesions

Notably, imaging has detection limits regarding size (as cysts are in principle the only visible precursor lesion) and do not detect precursor lesions in the form of PanINs, the most common precursor state to pancreatic cancer. However, pancreatic

cystic precursors, most often as IPMNs or premalignant mucinous cystic lesions, are detectable with imaging studies [29]. Currently, more patients are diagnosed with incidental pancreatic cysts, and despite available guidelines for surveillance or resection, there is considerable controversy towards the role of observation versus resection in a number of these lesions [30]. However, such cystic lesions may represent a viable risk group for exploring other biomarkers to assess risk and define progression from precursor to invasive cancer [31, 32], as discussed elsewhere in this book.

23.4 Metabolic Changes and Use of Metabolomics Targets in PDAC

New-onset diabetes and changes in fasting blood glucose is but one among several metabolic alterations that follow the progression of pancreatic cancer (Fig. 23.4) [17]. While fasting blood glucose may be a target based on the PDAC specific mechanisms to increased blood glucose, several other metabolic alterations occur in PDAC, involving muscle mass, lipids and protein synthesis [33–38].

Increased levels of branched-chain amino acids has been found years prior to diagnosis of PDAC in several studies, suggesting these to be metabolomic biomarkers for future PDAC risk [37, 39, 40]. In one study [40], elevated plasma levels of branched-chain amino acids (BCAAs) are associated with a greater than twofold increased risk of future pancreatic cancer diagnosis. This elevated risk was independent of known predisposing factors with the strongest association observed among subjects with samples collected 2–5 years before diagnosis of PDAC, when occult disease is probably present.

In an attempt at validating the findings, European cohort data (from Norway, Finland, Estonia and the Netherlands) did not support the branched-chain amino acids identified earlier in several US cohorts as potential biomarkers for pancreatic cancer [41]. The European cohorts identified glutamine and histidine as potential biomarkers of biological interest but concluded that the results imply that a study at this scale does not yield metabolomic biomarkers with sufficient predictive value to be clinically useful per se as prognostic biomarkers.

One problem with several of the biomarker studies is that the sample is collected at the time of PDAC diagnosis (or, even later after diagnosis) which may not correctly reflect the metabolomic profile year before a diagnosis is made. Similar experience has been made with other types of serum markers, including microRNA in serum [42].

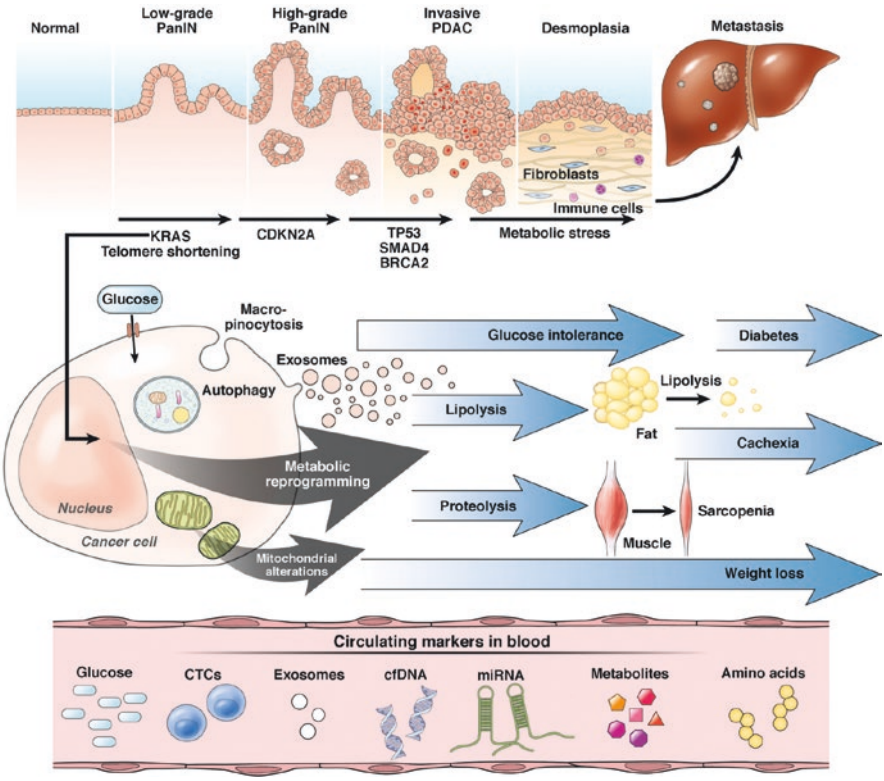

Fig. 23.4 Metabolic changes and circulating biomarkers for early detection. Pancreatic cancer progresses through morphologic changes (PanIN) that eventually progresses to invasive PDAC. Known genetic alterations occur with each step in the progression. Other alterations associated with stepwise progression may be less well-described. PDAC is further characterized by a strong desmoplastic reaction and an intricate crosstalk between cancer-cells and the surrounding fibroblasts and immune cells in the stroma that fosters progression, epithelial–mesenchymal transition, and eventually metastasis. Pancreatic cancer cells are also characterized by a KRAS-driven extensive metabolic reprogramming. This eventually leads to the clinical phenotype of weight loss, diabetes, sarcopenia, and cachexia often seen in patients with pancreatic cancer. Assuming that these molecular processes may occur earlier in carcinogenesis and, thus, may potentially be excreted in the circulating blood (bottom part), the identification of such sensitive markers may eventually help to facilitate earlier diagnosis of pancreatic cancer at a curable stage. *CTCs* circulating tumor cells, *cfDNA* cell-free DNA, *miRNA* microRNA, *PanIN* pancreatic intraepithelial neoplasia, *PDAC* pancreatic adenocarcinoma. (Reproduced from Soreide K. Sweet Predictions Speak Volumes for Early Detection of Pancreatic Cancer. Gastroenterology 2018;155(2):265–268 with permission from Elsevier © 2018)

23.5 Biomarkers for Early Detection of PDAC

The promise of biomarkers and the 'omics' technology have yet to make its major breakthrough in early cancer detection in general [13], and possibly more so when it comes to pancreatic cancer. One may only look to prevalence cancers such as breast, prostate, colorectal and lung cancer to realize the immense research focus over the past decades, with slow return on investment overall.

Development of biomarkers that generate clinically useful information that could change the course of the disease for a patient, is a multiphase collaboration between various stakeholders, such as, academia, funding agencies, health-care providers, reimbursement organizations or authorities and commercial companies [43]. Such research must be carefully planned in order to focus on what clinical questions the biomarkers should address (e.g. for screening? diagnostics? predictive or prognostic?). The clinical question being addressed will have direct implications for sample acquisition, including necessary clinical documentation, as well as pre-analytical variables that might act as confounding factors [18, 43–47]. However, biomarkers of clinical utility all relate to an ability to deliver accurate and improved diagnostic information to the clinicians.

23.5.1 Available Panels and Criteria for Early Detection of PDAC

A huge number of suggested and promising biomarkers and panels exist in the available literature, with few if any having reached clinical use. The *Alliance of Pancreatic Cancer Consortia for Biomarkers for Early Detection* provide a common platform and the resources necessary for validation of available markers felt to be promising for further pursuit [48]. The consensus group evaluated all existing panels (up to 2016) for early detection of PDAC in a workshop using specific criteria for evaluating the panels (Box 23.4).

The panel evaluated three groups of markers; genomic, proteomic and imaging markers.

Although none of the biomarkers evaluated seemed to be ready for a large-scale biomarker validation trial, a number of them had sufficiently high sensitivity and specificity to warrant additional research, especially if combined with other

Box 23.4 Criteria for Panels Developed for Early Detection of PDAC

- Is the ***study design*** appropriate for the intended clinical application?
- Are data split into separate ***training*** and ***validation*** samples?
- What is the reported ***performance*** of the marker?
- What was the ***comparison group***?
- What was the ***sample size*** for training and validation groups?

biomarkers to form a panel [48]. The group was said to reconvene after 2 years, yet no further report on their continued evaluation is available at the time of writing.

23.6 Further Developments and Novel Technology

Some promising approaches are being investigated in the pursuit for non-invasive biomarkers that can be easily accessed or monitored, of which some will be briefly mentioned here.

23.6.1 Pancreatic Juice and Cyst Fluids

Detection of various biomarkers in pancreatic juice have been explored in several settings, including for high-risk subjects with familial risk or for patients with pancreatic cystic lesions. Both genomic and proteomic markers have been explored [49–53]. Many of these markers are evaluated in the context of pancreatic cysts [53] and described in more detail in those sections of this book. Both genomic, proteomic and metabolomic biomarkers are investigated in this context.

23.6.2 Saliva and Salivary Markers

Different combinations of metabolites, RNA and bacteria were found in human saliva in patients with and without PDAC [54, 55]. Analysis of the saliva transcriptome and metabolome seems to be the most promising avenue. The identification of an early salivary signature of PDAC is still in its infancy. However, some data exists that salivary miR-940 and miR-3679-5p are reliable markers for pancreatic cancer [56] as well as polyamines [55]. Other than being promising, these technologies and their accuracy needs further refinement before being introduced as useful clinical tests.

23.6.3 Urine-Test and Urinary Markers

Studies of cancer biomarkers in urine has increasingly received attention, also for PDAC [32, 57–60]. The attractive principle is a non-invasive, repeatable test which would allow for early detection of resectable PDAC. A three-marker panel in urine (using LYVE-1, REG1A, and TFF1 as candidate biomarkers) demonstrated promising accuracy [60]. When comparing PDAC stage I–II (n = 71) with healthy urine specimens, the panel achieved AUCs of 0.90 (95% CI, 0.84–0.96) and 0.93 (95%

CI, 0.84–1.00) in the training and validation datasets, respectively [60]. In PDAC stage I–II and healthy samples with matching plasma CA19-9, the panel achieved a higher AUC of 0.97 (95% CI, 0.94–0.99) than CA19.9 (AUC of 0.88). Adding plasma CA19.9 to the panel increased the AUC to 0.99, but did not improve the comparison of stage I-IIA PDAC (n = 17) with healthy urine [60]. The panel has since been evaluated in a PancRISK model [59], however still needs further evaluation to show efficacy as an early, non-invasive detection test for PDAC. Other studies have shown discriminative ability of urine markers, but with accuracy that currently does not permit use as a screening tool [58].

23.6.4 Imaging Tools and Radiomics

The core premise of radiomics is that the differences in size, shape, texture, and greyness of a tumor contoured from a radiological image can reflect the variations in histological phenotype and genotype of the tumor [53]. Briefly explained, various radiological images (typically CT or MRI scans) can be converted into mineable data through which high-throughput extraction of quantitative features can be done by computers. The extracted data can then be combined with the patients' clinical features to contrive a model that will improve the accuracy of a diagnostic or prognostic model for cancer or, even by means of adding artificial intelligence or machine learning allow for early detection of cancer [61].

23.6.5 Biosensors

Due to their advantages (sensitivity, specificity, noninvasiveness, short assay time, and cost effectiveness) over traditional analytical methods (PCR and ELISA), biosensors have received considerable interest in cancer diagnosis [62–65]. Biosensors are designed to detect a specific biological analyte by essentially converting a biorecognition event into a measurable signal that can be detected and analyzed. A typical biosensor consists of a *recognition element*, a *transducer*, and a *signal-processing unit* (signal output). Based on the working principle, the recognition elements used in biosensors can be DNA, antibodies, antigens, enzymes, peptides, aptamers, microorganisms, and ligands. The use of biosensors has already found wide-spread applications in society, such as in the food and fermentation industries, plant biology, in defense, marine science, drug discovery, and medical sciences.

In PDAC, there are a few reports investigating biosensors for detection of cancers [62, 63]. In one study [63], the investigators explored fluorescence nanobiosensors for ultrasensitive (sub-femtomolar) arginase and protease detection and found an enzymatic signature for the detection of PDAC in serum. However, the sample size was small and lacking internal and external validation.

23.6.6 Liquid Biopsies and Circulating Biomarkers

With the several metabolic alterations that follow the progression of pancreatic cancer (Fig. 23.4) [17] there has been an interest in exploring the circulation elements that may be derived from precursor lesions or pancreatic cancers, including genomic and proteomic biomarkers, including circulating tumor cells (CTCs) and exosomes, as well as cell free DNA (cfDNA) [66–73]. Such biomarkers have been used to demonstrate the ability to detect several tumor types at a generic level [74], with ability to diagnose at an early stage for when resection is possible [75]. One such test (CancerSEEK) detected early stage cancers, including PDAC, through assessment of the levels of circulating proteins and mutations in cell-free DNA [75]. Others have looked into multi-marker panels adding CA 19-9 to the panel and, hence, increasing the diagnostic accuracy [76].

In a meta-analysis of a total of 19 studies (with 1872 individuals) exploring liquid biopsies for diagnosis of PDAC [77], 7 were studies about ctDNA, 7 were on CTCs and 6 were about exosomes.

The pooled sensitivity estimates for ctDNA, CTCs and exosomes in detecting PDAC were 0.64 (95% CI 0.58–0.70), 0.74 (95% CI 0.68–0.79) and 0.93 (95% CI 0.90–0.95), respectively. The pooled specificity estimates were 0.92 (95% CI 0.88–0.95), 0.83 (95% CI 0.78–0.88) and 0.92 (95% CI 0.88–0.95), respectively. The area under curve (AUC) of the sROC for ctDNA, CTCs and exosomes in detecting PDAC were 0.95, 0.82, and 0.98, respectively. The overall sensitivity, specificity and AUC of the sROC curve for overall liquid biopsy in detecting PDAC were 0.80 (95% CI 0.77–0.82), 0.89 (95% CI 0.87–0.91) and 0.95, respectively.

This meta-analysis confirmed that liquid biopsy had high diagnostic value in detecting PDAC, with exosomes showed highest sensitivity and specificity [77]. It is clear that such markers and technology have a huge potential for improved, early cancer detection, but further work is required before entering clinical routine practice as a routine diagnostic tool.

23.7 Conclusion

There are still several impediments and barriers to the ideal biomarker panel or modality for early detection of PDAC. Some of the novel biomarkers, inventive technology and their accuracy for detection may see translation to implementation for routine clinical use in the near future. It remains undetermined how to translate available and emerging omics techniques and omics platforms into prediction and early diagnosis for PDAC in order to best reduce the high number of deaths from this usually advanced disease. However, more effective and specific biomarkers for patients with early-stage PDAC are critically needed to allow an earlier diagnosis and detection at a curable stage.

References

1. Nicholson BD, Hamilton W, O'Sullivan J, Aveyard P, Hobbs FR. Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis. Br J Gen Pract. 2018;68(670):e311–e22. https://doi.org/10.3399/bjgp18X695801.
2. Risch HA, Yu H, Lu L, Kidd MS. Detectable symptomatology preceding the diagnosis of pancreatic cancer and absolute risk of pancreatic cancer diagnosis. Am J Epidemiol. 2015;182(1):26–34. https://doi.org/10.1093/aje/kwv026.
3. Klein AP, Lindstrom S, Mendelsohn JB, Steplowski E, Arslan AA, Bueno-de-Mesquita HB, et al. An absolute risk model to identify individuals at elevated risk for pancreatic cancer in the general population. PLoS One. 2013;8(9):e72311. https://doi.org/10.1371/journal.pone.0072311.
4. Boursi B, Finkelman B, Giantonio BJ, Haynes K, Rustgi AK, Rhim AD, et al. A clinical prediction model to assess risk for pancreatic cancer among patients with new-onset diabetes. Gastroenterology. 2017;152(4):840–50.e3. https://doi.org/10.1053/j.gastro.2016.11.046.
5. Sharma A, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, et al. Model to determine risk of pancreatic cancer in patients with new-onset diabetes. Gastroenterology. 2018;155(3):730–9.e3. https://doi.org/10.1053/j.gastro.2018.05.023.
6. Takeda Y, Saiura A, Takahashi Y, Inoue Y, Ishizawa T, Mise Y, et al. Asymptomatic pancreatic cancer: does incidental detection impact long-term outcomes? J Gastrointest Surg. 2017;21(8):1287–95. https://doi.org/10.1007/s11605-017-3421-2.
7. Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology. 2018;18(1):61–7. https://doi.org/10.1016/j.pan.2017.11.007.
8. Bretthauer M, Kalager M. Principles, effectiveness and caveats in screening for cancer. Br J Surg. 2013;100(1):55–65. https://doi.org/10.1002/bjs.8995.
9. Moutinho-Ribeiro P, Coelho R, Giovannini M, Macedo G. Pancreatic cancer screening: still a delusion? Pancreatology. 2017;17(5):754–65. https://doi.org/10.1016/j.pan.2017.07.001.
10. Torphy RJ, Schulick RD. Screening of patients at risk for familial pancreatic cancer: what is beneficial? Surg Clin North Am. 2018;98(1):25–35. https://doi.org/10.1016/j.suc.2017.09.003.
11. Henrikson NB, Aiello Bowles EJ, Blasi PR, Morrison CC, Nguyen M, Pillarisetty VG, et al. Screening for pancreatic cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;322(5):445–54. https://doi.org/10.1001/jama.2019.6190.
12. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Screening for pancreatic cancer: US Preventive Services Task Force reaffirmation recommendation statement. JAMA. 2019;322(5):438–44. https://doi.org/10.1001/jama.2019.10232.
13. Hartwell L, Mankoff D, Paulovich A, Ramsey S, Swisher E. Cancer biomarkers: a systems approach. Nat Biotechnol. 2006;24(8):905–8. https://doi.org/10.1038/nbt0806-905.
14. Ghatnekar O, Andersson R, Svensson M, Persson U, Ringdahl U, Zeilon P, et al. Modelling the benefits of early diagnosis of pancreatic cancer using a biomarker signature. Int J Cancer. 2013;133(10):2392–7. https://doi.org/10.1002/ijc.28256.
15. Joergensen MT, Gerdes AM, Sorensen J, Schaffalitzky de Muckadell O, Mortensen MB. Is screening for pancreatic cancer in high-risk groups cost-effective? - experience from a Danish national screening program. Pancreatology. 2016;16(4):584–92. https://doi.org/10.1016/j.pan.2016.03.013.
16. Corral JE, Das A, Bruno MJ, Wallace MB. Cost-effectiveness of pancreatic cancer surveillance in high-risk individuals: an economic analysis. Pancreas. 2019;48(4):526–36. https://doi.org/10.1097/mpa.0000000000001268.
17. Soreide K. Sweet predictions speak volumes for early detection of pancreatic cancer. Gastroenterology. 2018;155(2):265–8. https://doi.org/10.1053/j.gastro.2018.06.054.
18. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: opportunities and challenges. Gastroenterology. 2019;156(7):2024–40. https://doi.org/10.1053/j.gastro.2019.01.259.

19. Blackford AL, Canto MI, Klein AP, Hruban RH, Goggins M. Recent trends in the incidence and survival of stage 1A pancreatic cancer: a surveillance, epidemiology, and end results analysis. J Natl Cancer Inst. 2020; https://doi.org/10.1093/jnci/djaa004.
20. Exarchakou A, Papacleovoulou G, Rous B, Magadi W, Rachet B, Neoptolemos JP, et al. Pancreatic cancer incidence and survival and the role of specialist centres in resection rates in England, 2000 to 2014: a population-based study. Pancreatology. 2020;20:454–61. https://doi.org/10.1016/j.pan.2020.01.012.
21. Goggins M. Circulating biomarkers to identify patients with resectable pancreatic cancer. J Natl Cancer Inst. 2017;109(8). https://doi.org/10.1093/jnci/djx004.
22. Lu C, Xu CF, Wan XY, Zhu HT, Yu CH, Li YM. Screening for pancreatic cancer in familial high-risk individuals: a systematic review. World J Gastroenterol. 2015;21(28):8678–86. https://doi.org/10.3748/wjg.v21.i28.8678.
23. Sharma A, Chari ST. Pancreatic cancer and diabetes mellitus. Curr Treat Options Gastroenterol. 2018;16(4):466–78. https://doi.org/10.1007/s11938-018-0197-8.
24. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST. Fasting blood glucose levels provide estimate of duration and progression of pancreatic cancer before diagnosis. Gastroenterology. 2018;155(2):490–500.e2. https://doi.org/10.1053/j.gastro.2018.04.025.
25. Liao WC, Tu YK, Wu MS, Lin JT, Wang HP, Chien KL. Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. BMJ. 2015;350:g7371. https://doi.org/10.1136/bmj.g7371.
26. Toft J, Hadden WJ, Laurence JM, Lam V, Yuen L, Janssen A, et al. Imaging modalities in the diagnosis of pancreatic adenocarcinoma: a systematic review and meta-analysis of sensitivity, specificity and diagnostic accuracy. Eur J Radiol. 2017;92:17–23. https://doi.org/10.1016/j.ejrad.2017.04.009.
27. Li XZ, Song J, Sun ZX, Yang YY, Wang H. Diagnostic performance of contrast-enhanced ultrasound for pancreatic neoplasms: a systematic review and meta-analysis. Dig Liver Dis. 2018;50(2):132–8. https://doi.org/10.1016/j.dld.2017.10.012.
28. Corral JE, Mareth KF, Riegert-Johnson DL, Das A, Wallace MB. Diagnostic yield from screening asymptomatic individuals at high risk for pancreatic cancer: a meta-analysis of cohort studies. Clin Gastroenterol Hepatol. 2019;17(1):41–53. https://doi.org/10.1016/j.cgh.2018.04.065.
29. Canto MI, Almario JA, Schulick RD, Yeo CJ, Klein A, Blackford A, et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology. 2018;155(3):740–51.e2. https://doi.org/10.1053/j.gastro.2018.05.035.
30. Aunan JR, Jamieson NB, Soreide K. Observation or resection of pancreatic intraductal papillary mucinous neoplasm: an ongoing tug of war. World J Gastrointest Oncol. 2019;11(12):1092–100. https://doi.org/10.4251/wjgo.v11.i12.1092.
31. Gaiser RA, Pessia A, Ateeb Z, Davanian H, Fernandez Moro C, Alkharaan H, et al. Integrated targeted metabolomic and lipidomic analysis: a novel approach to classifying early cystic precursors to invasive pancreatic cancer. Sci Rep. 2019;9(1):10208. https://doi.org/10.1038/s41598-019-46634-6.
32. Yip-Schneider MT, Soufi M, Carr RA, Flick KF, Wu H, Colgate CL, et al. Performance of candidate urinary biomarkers for pancreatic cancer - correlation with pancreatic cyst malignant progression? Am J Surg. 2019;219:492–5. https://doi.org/10.1016/j.amjsurg.2019.09.013.
33. Moore HB, Culp-Hill R, Reisz JA, Lawson PJ, Sauaia A, Schulick RD, et al. The metabolic time line of pancreatic cancer: opportunities to improve early detection of adenocarcinoma. Am J Surg. 2019;218(6):1206–12. https://doi.org/10.1016/j.amjsurg.2019.08.015.
34. Khalaf N, Wolpin BM. Metabolic alterations as a signpost to early pancreatic cancer. Gastroenterology. 2019;156(6):1560–3. https://doi.org/10.1053/j.gastro.2019.03.028.
35. Sah RP, Sharma A, Nagpal S, Patlolla SH, Sharma A, Kandlakunta H, et al. Phases of metabolic and soft tissue changes in months preceding a diagnosis of pancreatic ductal adenocarcinoma. Gastroenterology. 2019;156(6):1742–52. https://doi.org/10.1053/j.gastro.2019.01.039.
36. Danai LV, Babic A, Rosenthal MH, Dennstedt EA, Muir A, Lien EC, et al. Altered exocrine function can drive adipose wasting in early pancreatic cancer. Nature. 2018;558(7711):600–4. https://doi.org/10.1038/s41586-018-0235-7.

37. Mayers JR. Metabolic markers as cancer clues. Science. 2017;358(6368):1265. https://doi.org/10.1126/science.aar2001.
38. Mehta KY, Wu HJ, Menon SS, Fallah Y, Zhong X, Rizk N, et al. Metabolomic biomarkers of pancreatic cancer: a meta-analysis study. Oncotarget. 2017;8(40):68899–915. https://doi.org/10.18632/oncotarget.20324.
39. Katagiri R, Goto A, Nakagawa T, Nishiumi S, Kobayashi T, Hidaka A, et al. Increased levels of branched-chain amino acid associated with increased risk of pancreatic cancer in a prospective case-control study of a large cohort. Gastroenterology. 2018;155(5):1474–82.e1. https://doi.org/10.1053/j.gastro.2018.07.033.
40. Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 2014;20(10):1193–8. https://doi.org/10.1038/nm.3686.
41. Fest J, Vijfhuizen LS, Goeman JJ, Veth O, Joensuu A, Perola M, et al. Search for early pancreatic cancer blood biomarkers in five European prospective population biobanks using metabolomics. Endocrinology. 2019;160(7):1731–42. https://doi.org/10.1210/en.2019-00165.
42. Franklin O, Jonsson P, Billing O, Lundberg E, Ohlund D, Nystrom H, et al. Plasma microRNA alterations appear late in pancreatic cancer. Ann Surg. 2018;267(4):775–81. https://doi.org/10.1097/sla.0000000000002124.
43. Borrebaeck CA. Precision diagnostics: moving towards protein biomarker signatures of clinical utility in cancer. Nat Rev Cancer. 2017;17(3):199–204. https://doi.org/10.1038/nrc.2016.153.
44. Wei L, Yao K, Gan S, Suo Z. Clinical utilization of serum- or plasma-based miRNAs as early detection biomarkers for pancreatic cancer: a meta-analysis up to now. Medicine (Baltimore). 2018;97(35):e12132. https://doi.org/10.1097/md.0000000000012132.
45. Long NP, Yoon SJ, Anh NH, Nghi TD, Lim DK, Hong YJ, et al. A systematic review on metabolomics-based diagnostic biomarker discovery and validation in pancreatic cancer. Metabolomics. 2018;14(8):109. https://doi.org/10.1007/s11306-018-1404-2.
46. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223–38. https://doi.org/10.1038/nrc.2017.7.
47. Kalinich M, Haber DA. Cancer detection: seeking signals in blood. Science. 2018;359(6378):866–7. https://doi.org/10.1126/science.aas9102.
48. Young MR, Wagner PD, Ghosh S, Rinaudo JA, Baker SG, Zaret KS, et al. Validation of biomarkers for early detection of pancreatic cancer: summary of the Alliance of pancreatic cancer consortia for biomarkers for early detection workshop. Pancreas. 2018;47(2):135–41. https://doi.org/10.1097/mpa.0000000000000973.
49. Okada T, Iwano H, Ono Y, Karasaki H, Sato T, Yamada M, et al. Utility of "liquid biopsy" using pancreatic juice for early detection of pancreatic cancer. Endosc Int Open. 2018;6(12):E1454–e61. https://doi.org/10.1055/a-0721-1747.
50. Takeda Y, Matsumoto K, Kurumi H, Koda H, Yamashita T, Onoyama T, et al. Efficacy and safety of pancreatic juice cytology by using synthetic secretin in the diagnosis of pancreatic ductal adenocarcinoma. Dig Endosc. 2018;30(6):771–6. https://doi.org/10.1111/den.13203.
51. Choi MH, Mejlaender-Andersen E, Manueldas S, El Jellas K, Steine SJ, Tjensvoll K, et al. Mutation analysis by deep sequencing of pancreatic juice from patients with pancreatic ductal adenocarcinoma. BMC Cancer. 2019;19(1):11. https://doi.org/10.1186/s12885-018-5195-7.
52. Nakamura S, Sadakari Y, Ohtsuka T, Okayama T, Nakashima Y, Gotoh Y, et al. Pancreatic juice exosomal microRNAs as biomarkers for detection of pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2019;26(7):2104–11. https://doi.org/10.1245/s10434-019-07269-z.
53. Carmicheal J, Patel A, Dalal V, Atri P, Dhaliwal AS, Wittel UA, et al. Elevating pancreatic cystic lesion stratification: current and future pancreatic cancer biomarker(s). Biochim Biophys Acta Rev Cancer. 1873;2020(1):188318. https://doi.org/10.1016/j.bbcan.2019.188318.
54. Sturque J, Berquet A, Loison-Robert LS, Ahossi V, Zwetyenga N. Interest of studying the saliva metabolome, transcriptome and microbiome in screening for pancreatic cancer. J Stomatol Oral Maxillofac Surg. 2019;120(6):554–8. https://doi.org/10.1016/j.jormas.2019.04.013.

55. Asai Y, Itoi T, Sugimoto M, Sofuni A, Tsuchiya T, Tanaka R et al. Elevated polyamines in saliva of pancreatic cancer. Cancers (Basel). 2018;10(2). https://doi.org/10.3390/cancers10020043.
56. Setti G, Pezzi ME, Viani MV, Pertinhez TA, Cassi D, Magnoni C et al. Salivary microRNA for diagnosis of cancer and systemic diseases: a systematic review. Int J Mol Sci. 2020;21(3). https://doi.org/10.3390/ijms21030907.
57. Bax C, Lotesoriere BJ, Sironi S, Capelli L. Review and comparison of cancer biomarker trends in urine as a basis for new diagnostic pathways. Cancers (Basel). 2019;11(9). https://doi.org/10.3390/cancers11091244.
58. Nissinen SI, Roine A, Hokkinen L, Karjalainen M, Venalainen M, Helminen H, et al. Detection of pancreatic cancer by urine volatile organic compound analysis. Anticancer Res. 2019;39(1):73–9. https://doi.org/10.21873/anticanres.13081.
59. Blyuss O, Zaikin A, Cherepanova V, Munblit D, Kiseleva EM, Prytomanova OM, et al. Development of PancRISK, a urine biomarker-based risk score for stratified screening of pancreatic cancer patients. Br J Cancer. 2020;122(5):692–6. https://doi.org/10.1038/s41416-019-0694-0.
60. Radon TP, Massat NJ, Jones R, Alrawashdeh W, Dumartin L, Ennis D, et al. Identification of a three-biomarker panel in urine for early detection of pancreatic adenocarcinoma. Clin Cancer Res. 2015;21(15):3512–21. https://doi.org/10.1158/1078-0432.Ccr-14-2467.
61. Korn RL, Rahmanuddin S, Borazanci E. Use of precision imaging in the evaluation of pancreas cancer. Cancer Treat Res. 2019;178:209–36. https://doi.org/10.1007/978-3-030-16391-4_8.
62. Qian L, Li Q, Baryeh K, Qiu W, Li K, Zhang J, et al. Biosensors for early diagnosis of pancreatic cancer: a review. Transl Res. 2019;213:67–89. https://doi.org/10.1016/j.trsl.2019.08.002.
63. Kalubowilage M, Covarrubias-Zambrano O, Malalasekera AP, Wendel SO, Wang H, Yapa AS, et al. Early detection of pancreatic cancers in liquid biopsies by ultrasensitive fluorescence nanobiosensors. Nanomedicine. 2018;14(6):1823–32. https://doi.org/10.1016/j.nano.2018.04.020.
64. Chen SL, Chen CY, Hsieh JC, Yu ZY, Cheng SJ, Hsieh KY et al. Graphene oxide-based biosensors for liquid biopsies in cancer diagnosis. Nanomaterials (Basel). 2019;9(12). https://doi.org/10.3390/nano9121725.
65. Ratajczak K, Stobiecka M. High-performance modified cellulose paper-based biosensors for medical diagnostics and early cancer screening: a concise review. Carbohydr Polym. 2020;229:115463. https://doi.org/10.1016/j.carbpol.2019.115463.
66. Miranda-Castro R, de-Los-Santos-Alvarez N, Lobo-Castanon MJ. Long noncoding RNAs: from genomic junk to rising stars in the early detection of cancer. Anal Bioanal Chem. 2019;411(19):4265–75. https://doi.org/10.1007/s00216-019-01607-6.
67. Gao Z, Jiang W, Zhang S, Li P. The state of the art on blood microRNAs in pancreatic ductal adenocarcinoma. Anal Cell Pathol (Amst). 2019;2019:9419072. https://doi.org/10.1155/2019/9419072.
68. Li G, Tang W, Yang F. Cancer liquid biopsy using integrated microfluidic exosome analysis platforms. Biotechnol J. 2020;2020:e1900225. https://doi.org/10.1002/biot.201900225.
69. Nordgard O, Tjensvoll K, Gilje B, Soreide K. Circulating tumour cells and DNA as liquid biopsies in gastrointestinal cancer. Br J Surg. 2018;105(2):e110–e20. https://doi.org/10.1002/bjs.10782.
70. Kamyabi N, Bernard V, Maitra A. Liquid biopsies in pancreatic cancer. Expert Rev Anticancer Ther. 2019;19(10):869–78. https://doi.org/10.1080/14737140.2019.1670063.
71. Locke WJ, Guanzon D, Ma C, Liew YJ, Duesing KR, Fung KYC, et al. DNA methylation cancer biomarkers: translation to the clinic. Front Genet. 2019;10:1150. https://doi.org/10.3389/fgene.2019.01150.
72. Loft M, Lee B, Tie J, Gibbs P. Clinical applications of circulating tumour DNA in pancreatic adenocarcinoma. J Pers Med. 2019;9(3). https://doi.org/10.3390/jpm9030037.
73. Lee JS, Park SS, Lee YK, Norton JA, Jeffrey SS. Liquid biopsy in pancreatic ductal adenocarcinoma: current status of circulating tumor cells and circulating tumor DNA. Mol Oncol. 2019;13(8):1623–50. https://doi.org/10.1002/1878-0261.12537.

74. Shen SY, Singhania R, Fehringer G, Chakravarthy A, Roehrl MHA, Chadwick D, et al. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature. 2018;563(7732):579–83. https://doi.org/10.1038/s41586-018-0703-0.
75. Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018;359(6378):926–30. https://doi.org/10.1126/science.aar3247.
76. Berger AW, Schwerdel D, Reinacher-Schick A, Uhl W, Algul H, Friess H, et al. A blood-based multi marker assay supports the differential diagnosis of early-stage pancreatic Cancer. Theranostics. 2019;9(5):1280–7. https://doi.org/10.7150/thno.29247.
77. Zhu Y, Zhang H, Chen N, Hao J, Jin H, Ma X. Diagnostic value of various liquid biopsy methods for pancreatic cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(3):e18581. https://doi.org/10.1097/md.0000000000018581.

Chapter 24
Clinical Presentation and Symptoms in Pancreatic Cancer

Florian Primavesi

Take Home Messages

- The majority of pancreatic cancer present after the fifth and sixth decade in life.
- Epigastric pain with radiation to the back, weight loss, painless jaundice or new-onset diabetes are worrisome features suggestive of pancreatic cancer.
- Exocrine and endocrine pancreatic insufficiency is frequently present at time of diagnosis.
- Tumour-associated thrombosis ("Trousseau Syndrome") is common in pancreatic cancer.
- A large variety of rare para-neoplastic syndromes are described in the literature.
- Validated risk calculators are freely available online for estimation of the individual likelihood of underlying pancreatic cancer in patients with concerning symptoms and medical history.

Pearls and Pitfalls

- Symptoms in patients with pancreatic cancer are often vague and unspecific, with a high incidence in the general population, leading to recurrent consultations to primary care.
- While long-standing diabetes mellitus itself is a risk factor for development of pancreatic malignancy, new-onset diabetes mellitus (type 3c) is also a common symptom of underlying, undiagnosed pancreatic cancer.
- Both acute and chronic pancreatitis may be associated with underlying pancreatic cancer.
- Pancreatic cancer is responsible for a high number of malignancy-related (paraneoplastic) thromboembolic events among patients with visceral malignancies.

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Future Perspectives

- Future algorithms incorporating not only clinical symptoms and medical history but also genetics and biomarkers will potentially allow to systematically screen high-risk populations and enhance early detection of pancreatic cancer.

24.1 Introduction

Most commonly the clinical presentation of pancreatic ductal adenocarcinoma (PDAC) includes unspecific symptoms, which explains to some part the often-late diagnosis and contributes to poor long-term survival rates [1, 2]. A study from the United Kingdom has shown, that in the year prior to PDAC diagnosis patients had already consulted their general practitioner on a median of 18 occasions [3]. This highlights, that many patients are initially falsely reassured by the intermittent or unspecific nature of their symptoms. Screening for pancreatic cancer of all patients with general abdominal symptoms is currently not feasible due to the lack of effective tests with sufficient sensitivity and specificity in this cohort with low lifetime risk, despite increasing incidence of PDAC in most countries [4]. However, there are pattern of worrisome clinical features ("red flags") that particularly warrant extensive application of diagnostic tests to rule out or confirm suspicion of pancreatic cancer.

24.2 Frequency of Different Symptoms

Frequently reported complaints of patients presenting with newly diagnosed PDAC are presented in Table 24.1 and Fig. 24.1.

The classical textbook symptom is painless jaundice due to an obstruction of the intrapancreatic common bile duct, which belongs to the most frequent clinical signs (about 35%) since more than 80% of tumours are located in the pancreatic head. In patients over 60 years, painless jaundice is caused by malignancies of the pancreas or the distal bile duct in about 20% of all cases. However, an even more common symptom is abdominal pain (>40%), most frequently located in the epigastric region and often with radiation into the back (30%), which is especially suspicious when long-lasting (>6 months) and combined with weight loss, decreased appetite or fatigue in patients >50 years of age. Other conditions often present in patients with pancreatic cancer are changes in bowel habits with maldigestion due to exocrine pancreatic insufficiency (about 35–50%) or new-/late-onset diabetes mellitus (>30%). Also, venous thromboembolism is a common finding in newly-diagnosed pancreatic cancer patients (>10%) and the frequency increases with extent and duration of the disease as well as patient-related factors such as platelet count,

Table 24.1 Common symptoms of pancreatic cancer at time of diagnosis

Symptoms	Frequency	Further characteristics
Abdominal pain	>40%	Usually epigastric and radiating into back. Increased level of suspicion in patients >50 years and when combined with decreased appetite, weight loss and fatigue.
Change in bowel habits, maldigestion, steatorrhea, weight loss	35–50%	Diarrhea, often associated with decreased appetite. Especially common in pancreatic head cancers or advanced tumours.
New-onset diabetes or impaired glucose-tolerance	30–80%	Especially suspicious in patients >50–60 years (late-onset diabetes). Frequently manifests within 1–3 years before cancer diagnosis.
Jaundice	35%	Most often painless and obstructive.
Back pain	30%	
Venous thromboembolism (VTE)	>10%	"Trousseau syndrome"—especially common in patients with metastatic disease, compression of vascular or lymphatic structures and history of previous VTE.
Fatigue/lethargy/depression	8%	
Acute pancreatitis	5%	The rate of malignancy in acute pancreatitis is about 1% in European and 6% in USA studies.
Supraclavicular lymphadenopathy, ascites, palpable abdominal mass	Rare	May indicate advanced disease.

Content based on data from [2, 3, 5–8]

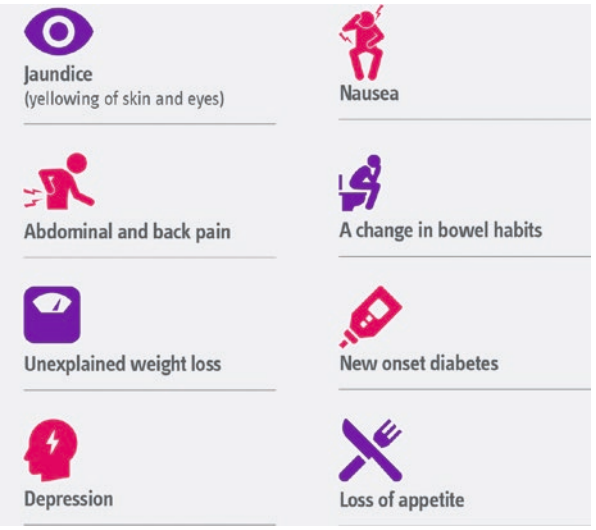

Fig. 24.1 Common symptoms in patients with newly diagnose pancreatic cancer. (Reproduced courtesy © UEG—United European Gastroenterology. https://www.ueg.eu/publications/)

Box 24.1 Armand Trousseau (1801–1867), French Internist

Trousseau's syndrome, or *Trousseau sign of malignancy*, also referred to as *thrombophlebitis migrans* or *migratory thrombophlebitis*, or *cancer-associated coagulopathy*, based on the observation by Trousseau over 150 years ago that thrombophlebitis or thromboembolic events may be associated with some cancers. The risk is highest in pancreatic cancer, gastric cancer and lung cancers.

(Image courtesy Bibliothèque nationale de France, open to public domain)

haemoglobin level or BMI. Cancer-related hypercoagulability in visceral malignancies is generally related to as the Trousseau syndrome (Box 24.1), and besides this common syndrome, there is a broad spectrum of rare tumour-associated paraneoplastic syndromes reported in PDAC.

The following paragraphs provide an overview over the clinical picture of clinical symptoms in pancreatic cancer patients. Details on clinical application and typical patterns of patient-blood derived biomarkers ("tumour-markers"), interventional technique and imaging results are provided in other respective chapters of this textbook.

24.3 Jaundice

Jaundice, especially when painless and present in elderly patients without obvious biliary stones, should always raise concern regarding underlying malignancies of the bile duct, the pancreas or the ampulla of Vateri. Therefore, extensive diagnostics including imaging (CT, MRI) and endoscopy (EUS, ERCP) must be applied until sufficient clinical certainty can be achieved to rule out or confirm suspicion.

In general, jaundice is present in about 35% of patients with pancreatic cancer, but the frequency in periampullary tumours is significantly higher at about 65%, due to the anatomic location.

Jaundice is often accompanied by weight loss, pruritus and deranged liver function tests mainly depending on the severity and duration of biliary duct obstruction [9]. Although the presence of jaundice is commonly considered to lead to earlier diagnosis of malignancies involving the periampullary region, recent studies have shown that it is in fact associated with more advanced tumour characteristics (T- and N-stage, perineural invasion) and inferior oncological long-term outcome in resectable pancreatic head cancer patients. However, absence of jaundice was not associated with improved survival in non-resectable cases [9, 10].

24.4 Pancreatic Cancer in New-Onset Versus Long-Standing Diabetes Mellitus

The relationship between pancreatic cancer and diabetes mellitus represents a classical chicken or egg dilemma and there is on-going debate about a bi-directional association [6, 11]. Results of epidemiological studies have suggested, that patients with long-standing diabetes have an at least twofold increased risk to develop pancreatic cancer, but this may increase up to sevenfold with a diabetic disease history of >3 years [12]. On the other hand, the markedly raised risk for pancreatic cancer in patients with new-onset diabetes mellitus compared to healthy controls shows, that pancreatic cancer as a disease of the exocrine pancreas can itself also cause diabetes. Diabetes in this setting is classified as type 3c diabetes mellitus (T3cDM; Table 24.2).

Up to 80% of PDAC patients experience some degree of impaired glucose tolerance or diabetes. Recent studies have found, that in 70–80% their diabetes began within a year preceding the diagnosis of cancer, often before the tumour is radiologically detectable [13]. Intriguingly, T3cDM is also present in small malignant lesions, and compared to classical type 2 diabetes mellitus it often improves after pancreatic resection (in about 50% of patients). These facts and further basic science have provided compelling evidence for the theory that it could indeed be a consequence of a paraneoplastic syndrome rather than just consumption of functional pancreatic parenchyma.

Table 24.2 Classification of different types of diabetes

Type of diabetes	Underlying cause/manifestation
Type 1 diabetes	Autoimmune β-cell destruction, usually leading to absolute insulin deficiency. *Subtype*: LADA (latent autoimmune diabetes in adults) with onset in adult age and slow loss of insulin secretion.
Type 2 diabetes	Progressive loss of adequate β-cell insulin secretion on the background of insulin resistance.
Gestational diabetes	Diabetes diagnosed in second or third trimester of pregnancy not clearly overt prior to gestation.
Specific types of diabetes due to other causes	• Due to disease of the exocrine pancreas (also termed pancreoprivic diabetes or T3cDM; e.g. due to pancreatic cancer, cystic fibrosis, pancreatitis). Distinct feature: concurrent loss of exocrine function. • Monogenic diabetes syndromes. • Drug- or chemical-induced diabetes (glucocorticoids, HIV/AIDS medication, etc.).

Content based on [21, 22]

Clinical signs suggestive of PDAC-related diabetes are age >65, absence of obesity, history of weight loss, worsening of glucose control after weight loss and lack of family history for diabetes or presence of family history for pancreatic cancer [14–18]. Recently, a model including three of these clinical factors (change in weight, change in blood glucose, age at onset of diabetes) has been proposed to aid with stratifying the individual risk for pancreatic cancer in patients with newly diagnosed diabetes mellitus (END-PAC Model) [19].

In regard to further evaluating differential diagnosis, the Hb1Ac in diabetic patients with pancreatic cancer has been reported to be higher than in non-malignant diabetes. However, the limited predictive value does not allow for implementation of Hb1Ac into clinical screening pathways as a tumour marker [4]. In contrast, adrenomedullin—a potential mediator of beta-cell dysfunction in T3cDM—could be a promising marker for early detection of PDAC in the future and is currently investigated in studies [12, 14].

In a recent study, patients with or without diabetes at the time-point of PDAC diagnosis presented with similar clinical features, tumour size and prognosis, therefore diabetes does not seem to contribute to earlier diagnosis of pancreatic cancer [20]. However, in a previous work, patients with diabetes showed a slightly higher rate of resectability [5]. To enhance outcomes of resectable PDAC patients with diabetes, perioperative optimization of glucose management should be part of the pre-habilitation process.

24.5 Maldigestion and Steatorrhea

Pancreatic exocrine insufficiency in pancreatic cancer patients is caused by functional incapacity of the pancreatic gland and obstruction of the pancreatic duct, leading to deficiency of digestive enzymes secreted into the duodenum [7]. Although

several indirect and direct tests are available for diagnosis, it is commonly assessed by measuring faecal elastase-1 (FE-1).

About 50% of all PDAC patients experience symptoms of maldigestion and exocrine insufficiency at the time-point of diagnosis, depending on the location and stage of the tumour. A systematic review including nine observational cohort studies with almost 700 cancer patients assessed before undergoing pancreatic resection showed, that the preoperative prevalence of exocrine insufficiency is highest in case of necessity of a total pancreatectomy (median 63%), followed by pancreatoduodenectomy (median 44%; range 42–47%) and distal pancreatectomy (20%; range 16–67%) [23]. This confirms, that primarily tumours located in the pancreatic head or large/multiple lesions with consecutive duct obstruction cause maldigestion/steatorrhea symptoms.

When exocrine insufficiency is assessed prospectively with a combination of the FE-1 test and evaluation of steatorrhea-related symptoms as well as body weight dynamics, the true incidence in advanced pancreatic head cancer is more than 50–60% and this steeply increases to over 90% within the first 2–3 months after diagnosis [24]. Interestingly, extremely low values of FE-1 (≤20 μg/g) are independently associated with worse survival, with a hazards ratio (HR) comparable to presence of metastases or low albumin [25]. Accordingly, the assessment of exocrine insufficiency in patients to undergo pancreatic surgery is nowadays increasingly evaluated in pre-habilitation programs and pancreatic enzyme replacement therapy might not only play an important role *after* but also *before* pancreatic resection [26–28].

24.6 Acute and Chronic Pancreatitis or Isolated Pancreatic Duct Stenosis

In a large nationwide Danish cohort study, more than 28,000 patients admitted with *acute* pancreatitis were evaluated regarding incidence of pancreatic cancer and only around 1% were found to have underlying malignancy. Predictors of pancreatic cancer included age >50 (highest risk in patients 56–70 years), new-onset chronic pancreatitis (HR 2.4) and diabetes (HR 1.9). Also, absence of biliary or alcohol-related diseases was associated with underlying malignancy [29]. A recent Danish population-based registry from the same group confirmed the cancer incidence of about 1% in acute pancreatitis patients but also showed a significantly higher rate of 6% in cases from the United States via SEER (Surveillance, Epidemiology and End Results) data analysis. In both countries, cancer patients with acute pancreatitis had lower prevalence of metastases at diagnosis, a higher resection rate and improved survival than those without pancreatitis [30].

Other studies described, that approximately 5% of all patients with *chronic* pancreatitis develop pancreatic cancer during their life, with a 13-fold higher relative-risk compared to the general population or controls according to pooled results from seven studies [4].

Given the relative low incidence of chronic pancreatitis with comparable high risk for development of cancer, screening in this group of patients could potentially be of value when effective tests become increasingly available. However, the clinical signs and imaging findings of chronic pancreatitis and PDAC often overlap and may hamper correct diagnosis. Therefore, development of new accurate biomarkers to distinguish between these two entities is urgently needed and a focus of on-going studies [31].

Regarding non-pancreatitis associated chronic ductal changes on imaging, localized solitary stenosis of the main pancreatic duct without a detectable mass, or intraductal papillary mucinous neoplasm (IPMN) only has a low predictive value (about 50%) for pancreatic cancer and careful evaluation ideally with EUS, pancreaticoscopy or pancreatic juice cytology is advisable [32].

24.7 Venous Thromboembolism

The Trousseau syndrome (named after the French internist Armand Trousseau 1801–1867 Box 24.1) represents the most classical paraneoplastic syndrome associated with pancreatic cancer (and many other malignancies) [33]. It describes a state of hypercoagulability linked to visceral cancers resulting in thrombotic events. Although it was initially described as a migratory thrombophlebitis, thrombosis occurs in many different variations such as deep vein thrombosis of the extremities, pulmonary thromboembolism, nonbacterial verrucous endocarditis, arterial thromboembolism or chronic disseminated intravascular coagulopathy (DIC).

Pulmonary embolism is found in autopsies of up to 40% of all patients with pancreatic cancer [34], and the overall risk of thrombotic events is a 6.1-fold higher than in the normal population ranking among the highest of all malignancies according to a large meta-analysis [35].

The rate of venous thromboembolism in newly-diagnosed pancreatic cancer patients exceeds 10% and may increase up to 50% or more in cases with a high ONKOTEV score (presences of metastases, previous history of thromboembolism, vascular or lymphatic compression, high Khorana score) [8, 36–38].

Besides thromboembolic events a number of cutaneous and melanocytic paraneoplastic syndromes as well as other even less frequent conditions such as atypical rheumatoid arthritis or nephrotic syndromes are associated with pancreatic cancer. Overall, the spectrum is very colourful and includes haematological, cutaneous, articular, neuromuscular, renal or even psychiatric syndromes [33].

24.8 Paraneoplastic Syndromes and Associated Conditions with Pancreatic Cancer

Table 24.3 gives an overview of these syndromes including their typical clinical manifestation signs. They may occur simultaneously with the detection of pancreatic cancer or during its progression, but in a subset of patients, they can precede the

Table 24.3 Endocrine, cutaneous, melanocytic and other paraneoplastic syndromes associated with pancreatic cancer

Disease	Clinical manifestation/remarks
Endocrine syndromes	
De-novo (T3cDM) diabetes mellitus	Bidirectional association
Non-islet cell tumour hypoglycemia (NICTH)	Extremely rare
Hypercalcemia	Extremely rare
Cutaneous/melanocytis syndromes	
Acanthosis nigricans and Tripe palms	Hyperpigmented papillomatosis and hyperkeratosis of the skin and mucosal membranes with rapid extensive progression Acanthosis on the palms
Acquired diffuse palmoplantar keratoderma	Uniform yellow, hyperkeratotic thickening of the skin
Pancreatogenic panniculitis	Tender, red, brownish subcutaneous nodules (affects 2–3% of pancreatic disease patients)
Sign of Leser-Trelaut	Rapid progression of seborrheic keratosis
Necrolytic migratory erythema	Erythematous papules, painful polycyclic plaques
Paraneoplastic pemphigus	Painful, ulcerative mucosal erosions, erythema of the skin
Dermatomyositis	Symmetric proximal myopathy with periorbital oedema, heliotrope rash, red macular rash, V sign, Gottron papules, erythematous to violaceous plaques, subcutaneous calcifications, photosensibility
Erythema nodosum	Painful, tender, erythematous subcutaneous nodule
Palmar fasciitis	Flexion deformity of the fingers, thickened palmar fascia
Bilateral diffuse uveal melanocytic proliferation	Uveal thickening, cataract formation, bilateral blindness
Other syndromes	
Atypical, rapid onset rheumatoid arthritis	Rare
Dermatomyositis, polymyositis	Rare association, can be reversible, usually precede the tumour detection
Paraneoplastic gastroparesis	Autoimmune destruction of the stomach nerve plexus
Opsoclonus	Uncontrolled, rapid, involuntary, multivectorial eye movements
Nephrotic syndromes	Respond well to steroid therapy
Cancer-associated retinopathy [39]	Extremely rare, primary tumour therapy potentially stops progression

Developed from [33]

diagnosis of pancreatic cancer or other abdominal malignancies (especially gastric cancer) by even months and therefore careful evaluation is indicated in cases with spontaneous venous thromboembolism, Acanthosis nigricans, Tripe palms, etc. However, most of these syndromes are not specific to pancreatic malignancies. Some are reversible after response to treatment of the primary pancreatic cancer and—when present—associated metastases.

24.9 Clinical Algorithms to Identify Patients at High Risk of Pancreatic Cancer

Algorithms incorporating clinical symptoms, patient characteristics and medical history have been proposed within the last years to define the risk for development of pancreatic cancer in patients presenting with new abdominal or gastrointestinal symptoms [40, 41]. Also, convenient online risk calculators are nowadays available to determine the estimated risk in individual cases (e.g. http://www.qcancer.org/pancreas) [41].

Most recently, enhanced clinical risk scores implementing multi-omics investigations (genomics and blood-based biomarkers) were introduced to further help with identifying high-risk populations and informing clinical decisions, but large-scale validation in terms of accuracy, reliability and cost-effectiveness is warranted [42].

24.10 Conclusion

Clinical presentation of pancreatic cancer is multifaceted with a variety of partly vague and unspecific symptoms. Due to the high incidence of some of these complaints (abdominal pain, maldigestion) in the general population, primary clinical screening is challenging. However, especially in elderly patients new-onset diabetes, weight-loss, painless jaundice as well as thromboembolic events are signs of particular concern for malignancy, and freely available clinical risk calculators can help to estimate the individual risk in primary care patients. Recently proposed algorithms incorporating not only clinical symptoms and medical history but also biomarkers will potentially allow systematically screening in high-risk populations in the future and hereby further enhance early detection of pancreatic cancer.

References

1. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846–61.
2. Poston GJ, D'Angelica M, Adam R. Surgical management of hepatobiliary and pancreatic disorders. 2nd ed. London: Informa Healthcare; 2010.
3. Keane MG, Horsfall L, Rait G, Pereira SP. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ Open. 2014;4(11):e005720.
4. Grote VA, Rohrmann S, Nieters A, Dossus L, Tjonneland A, Halkjaer J, et al. Diabetes mellitus, glycated haemoglobin and C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Diabetologia. 2011;54(12):3037–46.

5. DiMagno EP. Pancreatic cancer: clinical presentation, pitfalls and early clues. Ann Oncol. 1999;10(Suppl 4):140–2.
6. Magruder JT, Elahi D, Andersen DK. Diabetes and pancreatic cancer: chicken or egg? Pancreas. 2011;40(3):339–51.
7. Vujasinovic M, Valente R, Del Chiaro M, Permert J, Lohr JM. Pancreatic exocrine insufficiency in pancreatic cancer. Nutrients. 2017;9(3).
8. Godinho J, Casa-Nova M, Moreira-Pinto J, Simoes P, Paralta Branco F, Leal-Costa L, et al. ONKOTEV score as a predictive tool for thromboembolic events in pancreatic cancer-a retrospective analysis. Oncologist. 2020;25(2):e284–90.
9. Peng X, Jiao X, Zhao P, Zhu R, Sun Y, Zhou L. Influence of non-jaundice stage at diagnosis on clinicopathological features and long-term survival of patients with periampullary carcinomas. Medicine. 2019;98(45):e17673.
10. Nakata B, Amano R, Kimura K, Hirakawa K. Comparison of prognosis between patients of pancreatic head cancer with and without obstructive jaundice at diagnosis. Int J Surg. 2013;11(4):344–9.
11. Pezzilli R, Pagano N. Is diabetes mellitus a risk factor for pancreatic cancer? World J Gastroenterol. 2013;19(30):4861–6.
12. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol. 2013;10(7):423–33.
13. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009;10(1):88–95.
14. Aggarwal G, Ramachandran V, Javeed N, Arumugam T, Dutta S, Klee GG, et al. Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulin resistance in beta cells and mice. Gastroenterology. 2012;143(6):1510–7.e1.
15. Noy A, Bilezikian JP. Clinical review 63: diabetes and pancreatic cancer: clues to the early diagnosis of pancreatic malignancy. J Clin Endocrinol Metab. 1994;79(5):1223–31.
16. Huang BZ, Pandol SJ, Jeon CY, Chari ST, Sugar CA, Chao CR, et al. New-onset diabetes, longitudinal trends in metabolic markers, and risk of pancreatic cancer in a heterogeneous population. Clin Gastroenterol Hepatol. 2019;18(8):1812–1821.e7.
17. Mueller AM, Meier CR, Jick SS, Schneider C. Weight change and blood glucose concentration as markers for pancreatic cancer in subjects with new-onset diabetes mellitus: a matched case-control study. Pancreatology. 2019;19(4):578–86.
18. Mueller AM, Meier CR, Jick SS, Schneider C. The potential of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing diabetes mellitus: a case-control study. Pancreas. 2018;47(7):807–15.
19. Sharma A, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, et al. Model to determine risk of pancreatic cancer in patients with new-onset diabetes. Gastroenterology. 2018;155(3):730–9.e3.
20. Dehayem YM, Phelip JM, Kengne AP, Choukem SP, Benhamou PY, Halimi S. Impact of diabetes mellitus on clinical presentation and prognosis of pancreatic cancer. Ann Endocrinol. 2011;72(1):24–9.
21. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S14–31.
22. Roden M. [Diabetes mellitus: definition, classification and diagnosis]. Wien Klin Wochenschr. 2016;128(Suppl 2):S37–40.
23. Tseng DS, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas. 2016;45(3):325–30.
24. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol. 2014;48(5):e43–6.
25. Partelli S, Frulloni L, Minniti C, Bassi C, Barugola G, D'Onofrio M, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. Digest Liver Dis. 2012;44(11):945–51.

26. Nakajima H, Yokoyama Y, Inoue T, Nagaya M, Mizuno Y, Kadono I, et al. Clinical benefit of preoperative exercise and nutritional therapy for patients undergoing hepato-pancreato-biliary surgeries for malignancy. Ann Surg Oncol. 2019;26(1):264–72.
27. Ausania F, Senra P, Melendez R, Caballeiro R, Ouvina R, Casal-Nunez E. Prehabilitation in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. Rev Esp Enferm Dig. 2019;111(8):603–8.
28. Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018;164(5):1035–48.
29. Kirkegard J, Mortensen FV, Heide-Jorgensen U, Cronin-Fenton D. Predictors of underlying pancreatic cancer in patients with acute pancreatitis: a Danish nationwide cohort study. HPB. 2020;22(4):553–62.
30. Kirkegard J, Gaber C, Lund JL, Hinton SP, Ladekarl M, Heide-Jorgensen U, et al. Acute pancreatitis as an early marker of pancreatic cancer and cancer stage, treatment, and prognosis. Cancer Epidemiol. 2019;64:101647.
31. Chou CY, Chang CT, Chen CJ. Analytically validated protein biomarkers of chronic pancreatitis and pancreatic cancer for potential clinical diagnosis with mass spectrometry: Rapid Commun Mass Spectrom; 2019. https://doi.org/10.1002/rcm.8580.
32. Kanno Y, Koshita S, Ogawa T, Kusunose H, Masu K, Sakai T, et al. Predictive value of localized stenosis of the main pancreatic duct for early detection of pancreatic cancer. Clin Endosc. 2019;52(6):588–97.
33. Zalatnai A, Perjesi E, Galambos E. Much more than Trousseau syndrome. The broad spectrum of the pancreatic paraneoplastic syndromes. Pathol Oncol Res. 2018;24(1):1–10.
34. Ogren M, Bergqvist D, Wahlander K, Eriksson H, Sternby NH. Trousseau's syndrome - what is the evidence? A population-based autopsy study. Thromb Haemost. 2006;95(3):541–5.
35. Iodice S, Gandini S, Lohr M, Lowenfels AB, Maisonneuve P. Venous thromboembolic events and organ-specific occult cancers: a review and meta-analysis. J Thrombosis Haemostasis. 2008;6(5):781–8.
36. Cella CA, Di Minno G, Carlomagno C, Arcopinto M, Cerbone AM, Matano E, et al. Preventing venous thromboembolism in ambulatory cancer patients: the ONKOTEV study. Oncologist. 2017;22(5):601–8.
37. Dutia M, White RH, Wun T. Risk assessment models for cancer-associated venous thromboembolism. Cancer. 2012;118(14):3468–76.
38. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902–7.
39. Ghadiri N, Yang Y, Burton BJ. Cancer-associated retinopathy in ampullary pancreatic cancer. BMJ Case Rep. 2019;12(11).
40. Pang T, Ding G, Wu Z, Jiang G, Yang Y, Zhang X, et al. A novel scoring system to analyze combined effect of lifestyle factors on pancreatic cancer risk: a retrospective case-control study. Sci Rep. 2017;7(1):13657.
41. Hippisley-Cox J, Coupland C. Identifying patients with suspected pancreatic cancer in primary care: derivation and validation of an algorithm. Br J Gen Pract. 2012;62(594):e38–45.
42. Pang Y, Holmes MV, Chen Z, Kartsonaki C. A review of lifestyle, metabolic risk factors, and blood-based biomarkers for early diagnosis of pancreatic ductal adenocarcinoma. J Gastroenterol Hepatol. 2019;34(2):330–45.

Chapter 25
TNM Staging for Pancreatic Adenocarcinoma

Marcus Roalsø and Kjetil Søreide

Take Home Messages

- The TNM systems provides a clear and simple system for describing tumor disease as a part of the diagnostic workup.
- Staging according to the TNM-system provides a uniform framework for classification of tumor burden related to survival.
- The TNM eighth edition has allowed for subdivision of size-based (pT-stage) and nodal (pN) staging
- TNM system is useful for trial inclusion and comparison of results between studies.

Pearls and Pitfalls

- Objective size-based criteria and arterial involvement shows better correlation with survival.
- The subdivision of nodal disease has led to better prognostic stratification.
- There is no standard grading scheme for the extent of residual tumor in pancreatectomy specimens following neoadjuvant therapy.

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- Inconsistencies in the pathological classification and reporting of resection status (R-status) complicates comparative research.
- In the neoadjuvant era, it is unsure how precise the TNM system reflects actual tumor behavior.

Future Perspectives
- The added role of biomarkers, such as CA 19-9, to the current TNM-staging needs to be better understood.
- The role of consensus molecular subtypes to staging needs to be explored.
- A model of 'biological behaviour' to disease staging over a purely 'anatomical classification' is needed.
- A universally agreed tumor regression system after neodjuvant treatment is needed.
- Future additions from modern molecular biology techniques will help delineate patient subpopulations towards personalized medicine.

25.1 Introduction

The 5-year survival rate for pancreatic cancer is poor, with closely corresponding disease incidence and mortality [1, 2]. Surgical resection remains the only curative approach, with multimodal therapies improving outcomes [3, 4]. To accurately predict prognosis and decide appropriate treatment options, it is vital to describe the extent of the illness. Localized tumors have a higher survival rate compared with disseminated disease. In addition, prognostication directs the inclusion of patients in clinical studies and allows comparison of care between different institutions. The stratification in the correct prognostic stage group is therefore important for reliable care and patient information.

There are several systems in use to stage various cancers [5, 6]. The tumor, node and metastasis (TNM) staging system is regarded the most useful in a clinical setting and has largely displaced other classification tools (Fig. 25.1). Developed by the American Joint Committee on Cancer (AJCC), in collaboration with the Union for International Cancer Control (UICC), the AJCC TNM staging system classify tumors according to the size and proximity to surrounding tissue of the primary tumor (T), involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M) [7].

25.2 The TNM Staging System

Widely adopted worldwide, the eighth TNM staging system (Table 25.1) describes exocrine pancreatic tumors (the exocrine and endocrine pancreas is separated in the eighth TNM edition), comprised mainly (95%) of pancreatic ductal adenocarcinoma (PDAC). Well-differentiated neuroendocrine tumors belong to the classification of neuroendocrine tumors of the pancreas and are therefore categorize differently [8, 9]. Primary tumors (T-stage) classify according to size and peripancreatic attachment/invasion (Box 25.1).

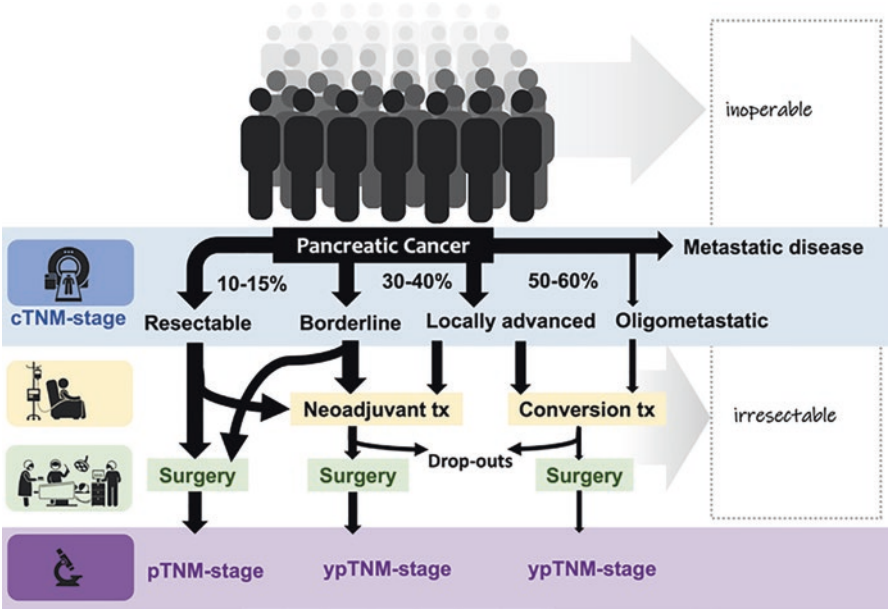

Fig. 25.1 Variation in clinical presentation and influence on staging in pancreatic cancer. 'Resectability' is a subjective measure with considerable variations between institutions, with differing definitions regarding borderline and locally advanced tumors. Neoadjuvant therapies are increasingly put into clinical practice in resectable cancers, but borderline tumors may still go to upfront surgery. Locally advanced cancers may be unresectable, but converted to exploration and resecgtion in some centres. Drop-outs (due to biological progression or clinical deterioration) is common, but not consistently reported. Additionally, evaluation of neoadjuvant therapies is unreliable on current imaging, and does not have a uniform system for grading on pathology. (Reproduced from Roalsø, Aunan, Søreide. (©2019 submitted))

Table 25.1 The TNM 8th edition AJCC prognostic stage groups

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Box 25.1 Definition of Primary Tumor (T-stage)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*[a]
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

[a]This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia

Box 25.2 Definition of Regional Lymph Node (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in ≥4 regional lymph nodes

Regional lymph nodes (N-stage) are assessed by the number of node metastases (Box 25.2). The number of histologically investigated lymph nodes are usually presented in brackets, with infiltrated/tumor positive nodes shown first and the total number second, e.g. pN1(2/12), pN2(5/12). Further, metastatic spread (M-stage) is noted if present or not.

25.2.1 TNM Descriptors

By convention, the T designation describes a tumor prior to any treatment. A set of prefixes signifies different time points in diagnosis or medical care (summarized in Box 25.3). The basis for the clinical classification is the initial radiological workup of patients, indicated by the "c" prefix (cTNM). The ensuing pathologic stage classification is designated by the "p" prefix (pTNM) and is based on gross and macroscopic examination of the resected tumor specimen (pT). pN describes surgically removed lymph nodes grossly and microscopically worked up for classification, while pM entails a microscopically proven tumor spread. The "m" suffix specifies multiple primary tumors in a single site, presented as T(m). Recurrent tumors after curative treatment and disease-free intervals are identified by the "r" prefix, while the "a" prefix signifies a tumor staged at autopsy.

Box 25.3 List of TNM Descriptors

Descriptor	Meaning
cTNM	Clinical staging of tumors based on multimodal imaging
pTNM	Gross and microscopic pathologic classification of surgically resected tumors
ycTNM	Clinical (re)staging during or after neoadjuvant therapy
ypTNM	Pathology staging after neoadjuvant therapy
rTNM	Recurrent tumor staged after a disease-free interval
aTNM	Tumor staged at autopsy

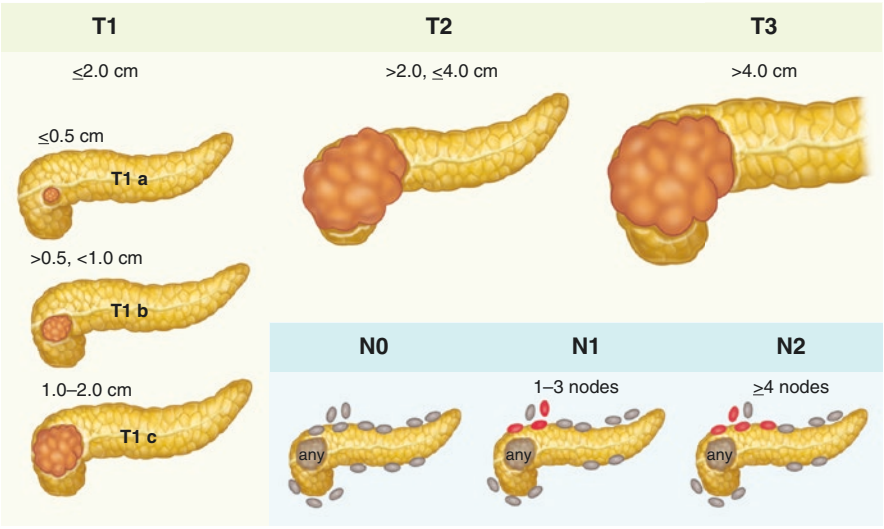

Fig. 25.2 Tumor and nodal classification of pancreatic cancer. The latest eighth AJCC TNM Staging system now subcategorize the smallest tumors (T1 ≤2 cm) into T1a, T1b and T1c based on size-criteria. Further, the N-category is now split into three groups, based on the number of positive lymph nodes

Patients being restaged after neoadjuvant or conversion therapy are designated with the prefix "y" to signify staging after treatment, with a designated ycTNM for clinical staging (e.g. imaging studies), or ypTNM classification for pathology staging after surgical resection after neoadjuvant treatment.

25.2.2 Changes in the Eighth Edition

First released in 1977 and subsequently updated every 5–7 years, there were no changes made in the 6th (2002) and 7th (2009) edition of the AJCC Cancer Staging Manual with regards to PDAC. The eighth edition released in October 2016 marked the first major revision of the T and N classification and is actively used in clinical practice since January 2018 (Fig. 25.2). In the present edition, the smallest tumors

Table 25.2 Comparison of the seventh and eighth edition of the TNM staging system

Category	Seventh edition	Eighth edition
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension	Tumor ≤2 cm in greatest dimension
T1a	–	Tumor ≤0.5 cm in greatest dimension
T1b	–	Tumor >0.5 cm and <1 in greatest dimension
T1c	–	Tumor 1–2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2 cm in greatest dimension	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
N1	Regional lymph node metastasis	Metastasis in 1–3 regional lymph nodes
N2	–	Metastasis in ≥4 regional lymph nodes

of the T1 type (≤2 cm) are now subcategorized into T1a, T1b and T1c based on size. Smaller tumors often have better outcomes. Previously, staging of T2 (>2 ≤ 4 cm) and T3 (>4 cm) tumors included extra-pancreatic extension. This can be difficult to define preoperatively, hence the T1-T3 categories are now purely size-based, demonstrating better correlation with survival [10]. In the prior seventh version, T4 tumors either involved the celiac axis or the superior mesenteric artery; or was a tumor considered unresectable by the diagnostic team. Surgical resectability relies on several hospital, patient and tumor-related factors, which inevitably will vary in-between institutions. Therefore, T4 tumors in the current edition relies solely on an objective measure of arterial involvement, disregarding the resectability appreciation. Additionally, the N category was split into N1 and N2, based on the number of positive lymph nodes. The new eighth edition developments are summarized in Table 25.2.

25.2.3 Prognostic Factors

The TNM staging system does not take resection margin (R) into account. Nevertheless, completeness of resection is of prognostic significance and current guidelines recommend its inclusion in the pathology report. R0 requires complete resection with grossly and microscopically negative margins >1 millimetre (mm). R1 includes grossly negative, but microscopically positive margins, while R2 means there is remnant tumor tissue (Box 25.4). A palliative resection with clear local margins, yet concomitant liver metastases left behind, also classify as R2 (and M+).

The resection limit depends on tumor extension at or within 1 mm of the margin. The most important boundary is the thin layer of connective tissue separating the

Box 25.4 Definition of Resection Category (R)

R category	R criteria
R0	Complete resection with grossly and microscopically negative margins of resection
R1	Grossly negative but microscopically positive margin(s) of resection
R2	Grossly and microscopically positive margin(s) of resection

Box 25.5 Histological Grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

uncinated process from the superior mesenteric artery. This area is at the highest risk of residual disease (up to 85% of positive margins) in cancers of the pancreatic head [11]. The AJCC does not consider other anatomic planes as true resection margins, however they are recommended to be included if present in the pathology report.

Histological grade has proven prognostic significance; with grade 3 poorly differentiated tumors having an unfavorable prognosis (Box 25.5) [12, 13]. The basis for the grading system is the World Health Organization (WHO) grading scheme, which includes glandular differentiation, mucin production, mitosis and nuclear pleomorphism. However, it is less predictive when considering patient outcomes compared to staging. Other histological features, such as perineural and lymphovascular invasion, are all detrimental to survival and therefore of potential interest in prognostication [14, 15].

25.3 Validation of the Eighth Edition

Upon publication, the data evaluating the changes in the eighth edition of The AJCC Cancer Staging Manual, were mainly based on a multi-institutional study from three centers in the United States [16]. The statistical data from the patients who had an R0 resection supported the proposed changes in cut offs. Multivariable analysis using recursive partitioning found statistically sound cut-offs for tumor size at <2.2 cm and ≥4.8 cm. This in line with the proposed limits of ≤2 cm (T1), >2 ≤ 4 cm (T2), and >4 cm (T3) in the eighth edition. In addition, cut-offs defining nodal stratification at >0.5 and ≥3.5 positive nodes were found. As defined in the eighth

edition, node negative (N0), 1–3 (N1) or ≥4 (N2) positive nodes stratification correlates statistically significantly with survival ($p < 0.001$) [16]. This is the same convention as in other gastrointestinal cancers.

The findings were then assessed using nationally representative registry data, using the Surveillance, Epidemiology and End Results (SEER) database (2004–2013) [17]. The eighth edition proved discriminatory abilities similar to that of the seventh edition but allowed for better stratification of patients with resected tumors, especially in regard to nodal involvement. The study revealed similar survival rates for patients staged as IIA (T3N0M0) or IIB (T1-3N1M0) until 20 months, before diverting. This suggests lymphatic spread has a delayed impact on survival, which in turn will be useful for stratifying patients after adjuvant and neoadjuvant treatments. However, based on recurrence patterns investigated in the randomized controlled ESPAC-4 trial, there was no survival difference regarding the pattern of recurrence, as either local or distant [18].

The multi-institutional and national studies called for further validation using an international cohort. Data derived from patients with resected pancreatic cancer from Europe and the United States, confirmed that the eighth edition provides a moderately increased prognostic accuracy in surgically treated patients, compared with the previous seventh edition [19]. In the eighth edition the concordance statistic was 0.57 compared to 0.55 in the previous edition, a minor increase. A value of 0.5 indicates the model is no better than random chance at predicting outcomes, while values >0.7 indicates a good model. Thus, the revised T stages were poorly associated with survival, especially in node-negative patients. As a group, the node-negative patients pose the greatest challenge in prognostication. However, the new N-stage was highly prognostic, showing accurate discrimination of survival with increasing nodal metastases.

25.4 Controversies in Clinical Practice

Primarily designed to assess the burden of disease, the TNM system currently fulfills several purposes, such as clinical guidance for cancer surveillance, eligibility for clinical trials, treatment allocation and prognostication. However, it is evident that other factors, including various aspects of tumor biology, molecular pathways and biological mechanisms contribute to prognosis [20, 21]. None of which are included in the current classification. Hence, it is important to recognize the inherent limitations of the TNM system's ability to predict patient outcomes [22].

In prior versions, nearly all cases of PDAC classified as extra-pancreatic tumors, mainly because the pancreas does not have a dense fibrous capsule deterring local cancer growth. This reduces the distribution of T stages and thus the predictive abilities of the TNM system [23]. The inclusion of size-based criteria in the eighth

edition groups patients more evenly among stages, without translation into an increased prognostic accuracy [16, 17]. Furthermore, reports of conflicting findings exist. Schlitter et al. reported that all four pT stages, as defined in the eighth edition, showed greatly improved discriminative power with significant overall differences in survival [24]. The latter study also found disagreeing data regarding lymph node status, where the N1 and N2 categories of the eighth edition resulted in no observed prognostic difference. This in contrast to prior findings, where the more subtle stratification of lymph node metastases appears to be prognostically significant [19].

Nevertheless, while the revised N stage appears prognostic for survival, the appropriate number of harvested lymph nodes after pancreatoduodenectomy is not agreed upon. A suitable amount of examined lymph nodes is important in order to prevent a stage migration effect due to missed lymph node metastases. At present, guidelines considers 12 lymph nodes as suitable for a pathology evaluation [25, 26]. However, a higher median number of examined nodes improves sub-staging and prognostic accuracy [23, 27].

The lymph node ratio (LNR) is the number of positive lymph nodes to the total number of lymph nodes removed. It is a strong prognostic factor in various cancer types, including PDAC [28]. However, the total number of positive lymph nodes have been shown to outperform LNR given a satisfactory amount of examined lymph nodes, which is why the N category now depends on the prior [27, 29]. This is in accordance with other gastrointestinal tumors.

While the number of examined lymph nodes may increase the detection of metastasis, the number of positive lymph node stations and their localization might further delineate survival characteristics. Certain lymph node stations are associated with poor survival, and para-aortic lymph node spread confers survival similar to M1 disease [30, 31]. In tumors of the head and neck of the pancreas, corresponding lymph nodes are located along the common hepatic artery, pyloric, posterior and anterior pancreatoduodenal arcades, common bile duct, portal vein, the superior mesenteric vein and right lateral wall of the superior mesenteric artery. In like manner, regional lymph nodes in tumors located in the body and tail, are adjacent to the celiac axis, common hepatic artery, splenic artery, and splenic hilum. The International Study Group on Pancreatic Surgery (ISGPS) does not recommend an extended lymphadenectomy as depicted in a recent consensus statement, as there is no apparent benefit to survival [32]. As a result, cancerous cells identified in other nodal groups, such as paraaortic lymph nodes, therefore classify as distant metastasis (M1) [33, 34]. However, a recent single-center study showed that one-third of patients with paraaortic lymph nodes metastasis experienced a survival prognosis comparable to that in between pN1 and pN2, staged according to the eighth AJCC TNM guidelines [35]. Therefore, curative resection in paraaortic lymph nodes metastasis might be warranted in select cases. However, the inclusion of localization characteristics would potentially add an undesirable layer of complexity to the relatively simple TNM classification.

25.4.1 The "R" Status

The resection margin status (R) is independently associated with survival [36]. Complete resection together with adjuvant therapy is a prerequisite for long time survival. Even so, to date there is no universally accepted pathological definition of the R-status for PDAC. In 2014 the International Study Group of Pancreatic Surgery (ISGPS) endorsed the definition proposed by The British Royal College of Pathologists (RCPath), which appears already favored in Europe [37]. In order to classify as R1, tumor cells have to be present directly at or within 1 mm from all seven designated resection margins (Fig. 25.3). As previously mentioned, the eighth edition of the AJCC TNM staging system does not include resection status, but considers the margin as positive if the tumor is at or within 1 mm (R1 $\leq$ 1 mm). However, it only takes the margin corresponding to the superior mesenteric artery

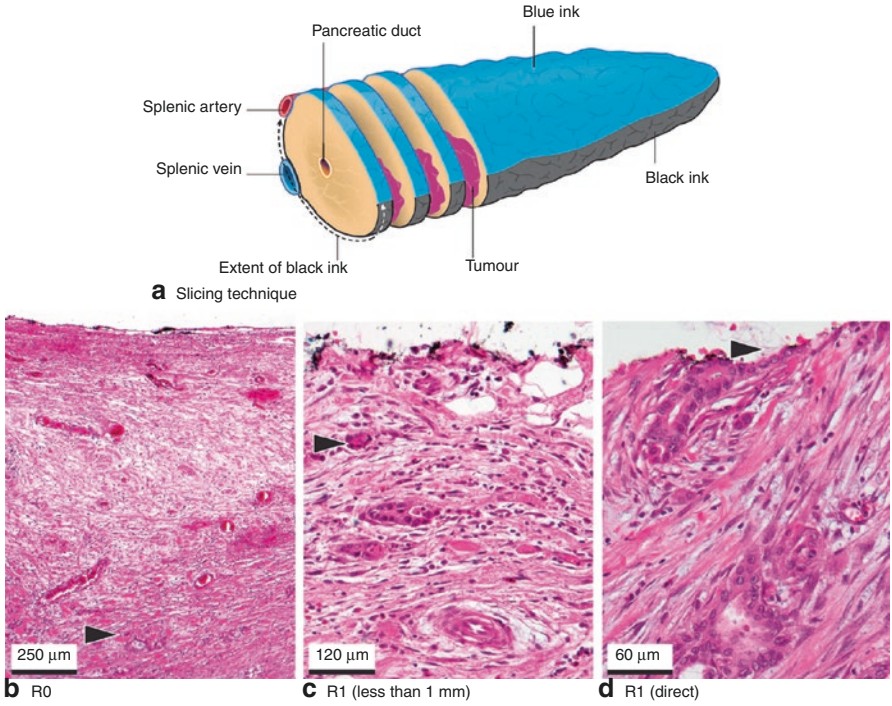

Fig. 25.3 Variation in R-classifications used in pancreatectomy. (**a**) Slicing and marking techniques for margin assessment in distal pancreatectomy specimens. Blue ink marks the anterior surface, while black ink marks the posterior part. The specimen is cut in 0.3–0.5 cm slices parallel to the transection margin. (**b**–**d**) Examples of resection margins (**b**) R0 > 1 mm (**c**) R1 <1 mm (**d**) R1 0 mm (direct). Black marker depicts cancer cells closest to the resection margin. (Reproduced from Hank, T., et al. Validation of at least 1 mm as cut-off for resection margins for pancreatic adenocarcinoma of the body and tail. Br J Surg 2018, 105: 1171–1181. https://doi.org/10.1002/bjs.10842, with permission from Wiley)

Box 25.6 Royal College of Pathologists Pancreatic Specimen Examination

Tumor clearance should be reported for the following designated margins:
1. Anterior
2. Posterior
3. Medial or superior mesenteric vein groove
4. Superior mesenteric artery
5. Pancreatic transaction
6. Bile duct
7. Enteric

into account, while the RCPath includes seven margins for tumor clearance in their protocol (Box 25.6). Therefore, the rates of tumor involvement vary significantly in the literature. Meta-analysis of radical resection rates show ranges in R0-status from 70 to 80% with a 0 mm margin, diminishing to 15–24% with a 1 mm margin [38]. This in turn affects the associated survival prognostics.

Strobel et al. investigated patients after pancreaticoduodenectomy for primary malignancies of the pancreatic head together with adjuvant therapy, in a prospective single center study, and found median and 5-year survival rates independently associated, in descending order, with a margin status of R0, R1 (<1 mm) or R1 (direct) [36]. Investigation of R-status and its prognostic role in patients undergoing resection for tumors in the pancreatic body and tail, demonstrated that the median and 5-year survival after R1 resection was less than half than that of patients with an R0 resection [39]. Consequently, a tumor free zone of ≤1 mm to define R0 is also relevant for body and tail cancers. This further supports the notion that the R-status should be reported with a margin of 1 mm. Nevertheless, the lack of a standardized pathology report complicates comparative research, which might delay the progress in the treatment of resectable tumors.

25.4.2 Staging after Neoadjuvant Treatment

After neoadjuvant treatment and subsequent surgical care, the grade/degree of regression (equal to tumor response) can be determined using the ypTNM staging. However, while there are several proposals, no single tumor regression grading system has been widely adopted [40, 41]. The College of American Pathologists (CAP) recommends a modified Ryan scheme as used in rectal cancers [42]. Here a tumor regression score of 0 equals to no visible viable cancer cells, representing a complete response. A near complete response, with single cells or rare groups of cancer cells present, is given a score of 1. Residual cancer with signs of tumor regression, but in lesser extent as in score 1, is considered a partial response and classified as score 2. No manifest tumor regression, or widespread residual cancer deems a poor to no response, resulting in a score of 3.

Using the prior seventh TNM edition, a study by Chatterjee et al. showed most tumors classified as pT3 before neoadjuvant therapy and as ypT3 after treatment, indicating no change [43]. This limited its use in the evaluation of treatment response. The study was then repeated using the eighth edition of the TNM system, in a cohort of 398 patients who underwent radical surgery after receiving neoadjuvant therapy [44]. Using the new size-based tumor criteria of the eighth edition, more than 90% of tumors previously classified as ypT3 using the seventh edition, reclassified as ypT1 (36%) and yPT2 (54.5%), compared to only 9.5% upholding ypT3. The latter was a significant predictor for poor overall survival, demonstrating that grading the extent of residual tumor is an important prognostic factor in PDAC.

25.4.3 Cancers within the Cells of the Pancreatic Duct

Depending on whether an intraductal papillary mucinous neoplasm (IPMN) is located in either the main-duct or in a branch-duct, the risk of malignant conversion varies between 57–92% and 6–46% respectively [45]. A mixed IPMN belongs to the former risk group. The tumor biology of invasive IPMN appears to differ from that of PDAC, with improved overall survival after resection [46]. Fan et al. validated the seventh and eighth edition of the AJCC Cancer Staging Manual in invasive IPMN, and found the seventh edition to be more applicable than the eighth edition [47]. This was due to differences in T staging, with stage IIA having a lower hazard ratio compared to stage IB in the eighth edition. Further, tumor size >2 cm was not a prognostic factor for patients with resectable IPMN. In addition, the changes in nodal status conferred no difference. Nevertheless, there is a need for prospective studies.

25.4.4 Current and Future Biomarkers

Other than the assigned T, N and M categories, the current TNM system requires no other prognostic factors for staging. However, cancer care increasingly includes biomarkers used for diagnosis, prognosis, and evaluation of treatment response, risk assessment and detection of recurrence.

The two most commonly used biomarkers in the diagnosis of pancreatic cancer are Carbohydrate Antigen 19-9 (CA 19-9) and Carcinoembryonic Antigen (CEA). Neither possess the test properties required for screening the general population [48, 49]. CA 19-9 is the only biomarker approved by the US Food and Drug Administration (FDA). Notably, up to 22% of the population do not express CA 19-9, varying depending on the genetic background [50]. Further, CA 19-9 increases in the setting of cholestasis in benign disease [51]. Hence, it carries less prognostic information in patients with biliary obstruction before an eventual decompression (e.g. by stent or bypass).

It is possible to detect both the two aforementioned antigens in tumors originating from different organ systems. Nevertheless, CA 19-9 positively correlate with a higher pathological stage, negatively correlate with survival and results in longer disease free survival when remaining within normal ranges post-resection [52, 53]. Serum CA 19-9 can also be used to monitor response of (neo-)adjuvant or conversion therapy for locally advanced tumors.

Currently, molecular profiling does not affect treatment strategies in PDAC. A classification system called consensus molecular subtypes (CMS) have identified four molecular subtypes in colorectal cancer [54]. This has revealed that colorectal cancer is a heterogenous disease, where molecular alterations predicts disease progress, response to treatment and prognosis. CMS is anticipated to constitute the basis for future clinical stratification and targeted interventions.

Delineating the molecular pathology in PDAC will likely result in a similar molecular taxonomy, enabling the identification of pancreatic cancer subtypes. This may lead to better differentiation of responders and non-responders to first-line therapies [55]. Large studies analyzing gene expression data in PDAC have identified distinct signatures from tumor- and microenvironment-specific samples [56, 57]. Further, Tuveson et al. elicited PDAC organoid models in order to perform drug sensitivity trials, identifying functional subtypes with corresponding gene expression signatures that predicts chemotherapy sensitivity [58]. Efforts to translate these gene expression classifications into clinical practice, early on in a patient's disease course, will be vital to the future of precision medicine in pancreatic cancer.

Mutant circulating tumor DNA (ctDNA) can be detected early on, even in resectable pancreatic tumors [59]. Furthermore, a liquid biopsy test detecting ctDNA for KRAS gene mutations, combined with other protein markers, identified nearly two-thirds of pancreatic tumors without evidence of distant metastasis [60]. Similar results have been found in exosome studies [61]. Increasingly sensitive and specific detection tools will conceivably result in non-invasive tests for early stage pancreatic malignancies [62]. Earlier identification of small tumors will potentially result in higher rates of R0 resection, perhaps at a stage prior to metastasis or more susceptible to adjuvant therapies, resulting in improved survival rates.

Whether such biomarkers will become part of future staging systems for PDAC, in order to incorporate tumor biology to predict cancer behavior and guide treatment remains to be investigated.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
2. Sun H, Ma H, Hong G, Sun H, Wang J. Survival improvement in patients with pancreatic cancer by decade: a period analysis of the SEER database, 1981–2010. Sci Rep. 2014;4:6747.
3. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr J-M, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology. 2015;15(1):8–18.

4. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg. 2019;270(2):340–7.
5. Gupta S, Aitken JF, Bartels U, Brierley J, Dolendo M, Friedrich P, et al. Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines. Lancet Oncol. 2016;17(4):e163–e72.
6. Bhatla N, Denny L. FIGO cancer report 2018. Int J Gynaecol Obstet. 2018;143(S2):2–3.
7. Amin MB, Edge SB. AJCC cancer staging manual. New York: Springer; 2017.
8. Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449(4):395–401.
9. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8.
10. Saka B, Balci S, Basturk O, Bagci P, Postlewait LM, Maithel S, et al. Pancreatic ductal adenocarcinoma is spread to the peripancreatic soft tissue in the majority of resected cases, rendering the AJCC T-stage protocol (7th edition) inapplicable and insignificant: a size-based staging system (pT1: </=2, pT2: >2-</=4, pT3: >4 cm) is more valid and clinically relevant. Ann Surg Oncol. 2016;23(6):2010–8.
11. Evans DB, Farnell MB, Lillemoe KD, Vollmer C, Strasberg SM, Schulick RD. Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1736–44.
12. Adsay NV, Basturk O, Bonnett M, Kilinc N, Andea AA, Feng J, et al. A proposal for a new and more practical grading scheme for pancreatic ductal adenocarcinoma. Am J Surg Pathol. 2005;29(6):724–33.
13. Giulianotti PC, Boggi U, Fornaciari G, Bruno J, Rossi G, Giardino D, et al. Prognostic value of histological grading in ductal adenocarcinoma of the pancreas. Int J Pancreatol. 1995;17(3):279–89.
14. Garcea G, Dennison A, Ong S, Pattenden C, Neal C, Sutton C, et al. Tumour characteristics predictive of survival following resection for ductal adenocarcinoma of the head of pancreas. Eur J Surg Oncol. 2007;33(7):892–7.
15. Chen JW, Bhandari M, Astill DS, Wilson TG, Kow L, Brooke-Smith M, et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. HPB (Oxford). 2010;12(2):101–8.
16. Allen PJ, Kuk D, Fernandez-del Castillo C, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg. 2017;265(1):185–91.
17. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) staging system for patients with pancreatic adenocarcinoma: a Surveillance, Epidemiology and End Results (SEER) analysis. Ann Surg Oncol. 2017;24(7):2023–30.
18. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019;154:1038–48.
19. Van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, De Pastena M, et al. International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg. 2018;153(12):e183617.
20. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
21. Ankeny J, Court C, Hou S, Li Q, Song M, Wu D, et al. Circulating tumour cells as a biomarker for diagnosis and staging in pancreatic cancer. Br J Cancer. 2016;114(12):1367–75.

22. O'Sullivan B, Brierley J, Byrd D, Bosman F, Kehoe S, Kossary C, et al. The TNM classification of malignant tumours—towards common understanding and reasonable expectations. Lancet Oncol. 2017;18(7):849–51.
23. Basturk O, Saka B, Balci S, Postlewait LM, Knight J, Goodman M, et al. Substaging of lymph node status in resected pancreatic ductal adenocarcinoma has strong prognostic correlations: proposal for a revised N classification for TNM staging. Ann Surg Oncol. 2015;22(3):1187–95.
24. Schlitter AM, Jesinghaus M, Jäger C, Konukiewitz B, Muckenhuber A, Demir IE, et al. pT but not pN stage of the 8th TNM classification significantly improves prognostication in pancreatic ductal adenocarcinoma. Eur J Cancer. 2017;84:121–9.
25. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006;13(9):1189–200.
26. Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA, Hines OJ, et al. Accuracy of staging node-negative pancreas cancer: a potential quality measure. Arch Surg. 2007;142(8):767–74.
27. Strobel O, Hinz U, Gluth A, Hank T, Hackert T, Bergmann F, et al. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. Ann Surg. 2015;261(5):961–9.
28. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg. 2011;254(2):311–9.
29. Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakashima A, et al. Number of metastatic lymph nodes, but not lymph node ratio, is an independent prognostic factor after resection of pancreatic carcinoma. J Am Coll Surg. 2010;211(2):196–204.
30. Malleo G, Maggino L, Capelli P, Gulino F, Segattini S, Scarpa A, et al. Reappraisal of nodal staging and study of lymph node station involvement in pancreaticoduodenectomy with the standard international study group of pancreatic surgery definition of lymphadenectomy for cancer. J Am Coll Surg. 2015;221(2):367–79.e4.
31. Komo T, Murakami Y, Kondo N, Uemura K, Hashimoto Y, Nakagawa N, et al. Prognostic impact of para-aortic lymph node micrometastasis in pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2016;23(6):2019–27.
32. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
33. Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg. 2007;94(3):265–73.
34. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012;19(3):230–41.
35. Hempel S, Plodeck V, Mierke F, Distler M, Aust DE, Saeger HD, et al. Para-aortic lymph node metastases in pancreatic cancer should not be considered a watershed for curative resection. Sci Rep. 2017;7(1):7688.
36. Strobel O, Hank T, Hinz U, Bergmann F, Schneider L, Springfeld C, et al. Pancreatic Cancer surgery. Ann Surg. 2017;265(3):565–73.
37. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88.
38. Chandrasegaram MD, Goldstein D, Simes J, Gebski V, Kench JG, Gill AJ, et al. Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. Br J Surg. 2015;102(12):1459–72.
39. Hank T, Hinz U, Tarantino I, Kaiser J, Niesen W, Bergmann F, et al. Validation of at least 1 mm as cut-off for resection margins for pancreatic adenocarcinoma of the body and tail. Br J Surg. 2018;105(9):1171–81.

40. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127(11):1335–9.
41. White RR, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA, et al. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. Ann Surg Oncol. 2005;12(3):214–21.
42. Ryan R, Gibbons D, Hyland J, Treanor D, White A, Mulcahy H, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology. 2005;47(2):141–6.
43. Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. Cancer. 2012;118(12):3182–90.
44. Chatterjee D, Katz MH, Foo WC, Sundar M, Wang H, Varadhachary GR, et al. Prognostic significance of new AJCC tumor stage in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant therapy. Am J Surg Pathol. 2017;41(8):1097–104.
45. Crippa S, Fernández-del Castillo C, Salvia R, Finkelstein D, Bassi C, Domínguez I, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clin Gastroenterol Hepatol. 2010;8(2):213–9.e4.
46. Wasif N, Bentrem DJ, Farrell JJ, Ko CY, Hines OJ, Reber HA, et al. Invasive intraductal papillary mucinous neoplasm versus sporadic pancreatic adenocarcinoma: a stage-matched comparison of outcomes. Cancer. 2010;116(14):3369–77.
47. Fan Z, Cheng H, Jin K, Gong Y, Huang Q, Xu J, et al. AJCC 7th edition staging classification is more applicable than AJCC 8th edition staging classification for invasive IPMN. World J Surg Oncol. 2019;17(1):137.
48. KIM JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol. 2004;19(2):182–6.
49. Meng Q, Shi S, Liang C, Liang D, Xu W, Ji S, et al. Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. Onco Targets Ther. 2017;10:4591–8.
50. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med. 2013;13(3):340–51.
51. Mann DV, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol. 2000;26(5):474–9.
52. Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol. 2012;23(7):1713–22.
53. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-del Castillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol. 2006;24(18).
54. Guinney J, Dienstmann R, Wang X, de Reynies A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015;21(11):1350–6.
55. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2019;16(4):207–20.
56. Puleo F, Nicolle R, Blum Y, Cros J, Marisa L, Demetter P, et al. Stratification of pancreatic ductal adenocarcinomas based on tumor and microenvironment features. Gastroenterology. 2018;155(6):1999–2013.e3.
57. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47(10):1168–78.
58. Tiriac H, Belleau P, Engle DD, Plenker D, Deschenes A, Somerville TDD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. Cancer Discov. 2018;8(9):1112–29.

59. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early-and late-stage human malignancies. Sci Transl Med. 2014;6(224):224ra24.
60. Cohen JD, Javed AA, Thoburn C, Wong F, Tie J, Gibbs P, et al. Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. Proc Natl Acad Sci. 2017;114(38):10202–7.
61. Allenson K, Castillo J, San Lucas F, Scelo G, Kim D, Bernard V, et al. High prevalence of mutant KRAS in circulating exosome-derived DNA from early-stage pancreatic cancer patients. Ann Oncol. 2017;28(4):741–7.
62. Lennon AM, Wolfgang CL, Canto MI, Klein AP, Herman JM, Goggins M, et al. The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia? Cancer Res. 2014;74(13):3381–9.

Chapter 26
Computed Tomography for Diagnosis and Staging in Pancreatic Cancer

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Take Home Messages
- A dedicated CT pancreatic protocol should be systematically evaluated, with a high spatial resolution, and using multiplanar reconstructions.
- CT is the imaging of choice for positive diagnosis and locoregional staging.
- CT should be systematically evaluated before any endoscopic procedure (ERCP or EUS guided biopsy) and placement of stents, so as not to interfere with the locoregional spread evaluation.

Pearls and Pitfalls
- A double duct dilatation sign should suggest cancer until proven otherwise, even if the lesion is not seen on CT.
- The pancreatic arterial phase is very important to obtain the best contrast between the pancreatic lesion which appears hypoattenuated compared to adjacent parenchyma, and so increase tumor conspicuity.
- The CT report must mention the retroportal pancreatic lamina, which is highly predictive of margin-positive surgical resection.

Future Perspectives
- The development of spectral CT should increase tumor conspicuity and consequently diagnostic performance.

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26.1 Introduction

Imaging is decisive in the initial management of patients with pancreatic malignancies. Computed tomography (CT) performed using modern techniques has become the key imaging method. CT must be performed routinely as part of both the pretreatment workup and the monitoring strategy of pancreatic adenocarcinoma. The goals of CT are to confirm the diagnosis and, most importantly, to assess the locoregional and distant spread in order to guide the treatment decisions.

In this chapter, the current use of CT for diagnosis and staging is discussed.

26.2 TNM Staging and Assessment of Resectability

The current staging classification for adenocarcinoma is TNM AJCC 2017 (eighth edition). Compared to the previous edition, there are a few modifications in the T (tumor size) and N (locoregional nodes) categories. The presence of distant positive nodes or of lesions at other distant sites (e.g., the peritoneum, liver, and/or lung) indicates metastatic disease (M category).

The assessment of resectability is chiefly useful for establishing the prognosis, as the results predict the likelihood of obtaining tumor-free margins (R0 resection) during resection [1]. CT is the main tool for assessing resectability due to its excellent diagnostic performance for predicting locoregional spread, notably to the blood vessels. The classification established by the NCCN [2] is the most widely used, while the MD Anderson [3] and 2017 ASCO [4] classifications are less often applied.

The resectability criteria differ across these classifications, notably regarding spread to the blood vessels, including the borderline resectable definitions (Table 26.1). In addition, the advent in recent years of neoadjuvant chemotherapy

Table 26.1 Staging according the NCCN classification

Vessels	Resectable	Borderline resectable	Unresectable
SMV/PV	No contact, <180 without vein contour irregularity	>180°, <180° with deformity or vein thrombosis but allowing safe and complete resection and reconstruction, contact with IVC	Unreconstructible obstruction, contact with most proximal draining jejunal branch
CHA	No arterial tumor contact	Contact without extension to celiac axis or HA bifurcation	Contact with extension to CA or CHA bifurcation
CA	No arterial tumor contact	No contact (head) Contact <180° (body and tail)	Contact >180, any contact with aorta
SMA	No arterial tumor contact	Contact <180°	Contact >180°, contact with first jejunal SMA branch, contact with aorta

SMV superior mesenteric vein, *PV* portal vein, *SMA* superior mesenteric artery, *CHA* common hepatic artery, *CA* celiac axis, *IVC* inferior vena cava, *HA* hepatic artery

has profoundly modified the treatment of pancreatic adenocarcinoma. Now, the goal is to identify not only those patients who can undergo immediate surgical resection but also those in whom neoadjuvant chemotherapy is expected to maximize the likelihood of achieving R0 resection. The term "borderline-resectable" is now used to designate tumors that may be resectable but whose spread to the blood vessels may result in incomplete resection in the event of primary surgery (Table 26.1).

26.3 Indications for Imaging Studies

CT is the only imaging study that must be performed routinely as part of the pretreatment workup of pancreatic tumors. The goal is to establish the diagnosis of pancreatic cancer and to assess locoregional and distant spread.

Ultrasonography has little to contribute. However, in patients who present with jaundice due to bile duct compression by a tumor in the head of the pancreas, ultrasonography is often the first-line imaging investigation.

Magnetic resonance imaging (MRI) has two main indications. In patients with an established diagnosis of potentially resectable pancreatic cancer, MRI of the liver with diffusion imaging and use of a liver-specific contrast agent, must be performed routinely to look for synchronous liver metastases, even when none are seen by CT [5, 6].

The presence of liver metastases contraindicates surgery (see the section on assessing distant spread). The other indication is a pancreatic lesion that is isoattenuating or not well delineated on the CT images. MRI of the pancreas with imaging of the bile duct and main pancreatic duct may help to delineate the tumor. The liver parenchyma should be assessed during the same investigation.

26.4 Standardized CT-Pancreas Protocol

A helical multidetector CT with thin slices (<1.5 mm) is used (Table 26.2). After an assessment of the native images, multiplanar reconstruction is performed to allow a more detailed analysis. To help identify the stomach and duodenum, the patient is asked to ingest about 200 mL of water 5–10 min before the beginning of the acquisition.

The images are acquired in three phases (Box 26.1): after an unenhanced acquisition, contrast material is injected intravenously and a pancreatic arterial acquisition followed by a portal phase acquisition are obtained. The recommended CT protocol for optimizing tumor detection and staging is detailed in Box 26.1 [7–9].

Table 26.2 Protocol for multidetector CT assessment of pancreatic cancer

Parameters	Details
Type of scanner	Helical (64 multidetector rows at least)
Section thickness	As thin as possible (<1 mm)
Interval same as section thickness	Axial
Oral contrast agent	Low-Hounsfeld units (water) or neutral oral contrast agents no positive
Intravenous contrast agent	High iodine concentration (300 mg I/mL) at an injection rate of 3–5 mL/s
Scan acquisition timing	Pancreatic parenchymal phase at 40–50 s; portal venous phase at 65–70 s
Image reconstruction and display	Axial 2–3-mm thickness, multiplanar reformats in the coronal plane at 2–3-mm thickness, MIP or 3D volumetric thick sections for vascular evaluation

From M. Zins, C. Matos and C. Cassinotto (Radiology 2018)

Box 26.1 Three Phase CT-Pancreas Protocol

1. Unenhanced acquisition

   Study of the abdomen

   The main goal is to identify the pancreatic gland in order to adjust the pancreatic helix. In addition, the images are examined for calcifications within the pancreatic parenchyma and/or evidence of hemorrhagic remodeling (seen as spontaneously high attenuation).
2. Pancreatic arterial acquisition

   The images are centered on the pancreas, with a reduced field of view in order to increase spatial resolution. An iodinated contrast agent containing 350 g of iodine/mL is injected in a dose of 1.5 mL/kg, at a rate of 3.5–4 mL/s. The acquisition is started 45–50 s after the beginning of the injection. The objective is to analyze the pancreatic gland and surrounding region. This phase is the key part of the protocol because, if performed appropriately, it provides the greatest contrast between the healthy pancreatic parenchyma and the tumor, thereby maximizing the chances of tumor detection. Good opacification of the upper mesenteric vein with persistent arterial opacification indicate that the pancreatic arterial acquisition is successful, that is, allows a detailed analysis of the blood vessels.
3. Portal phase acquisition

   This phase allows investigation of the abdomen and pelvis, and also of the lungs if deemed appropriate (detection of lung metastases). The acquisition is started 70–80 s after the beginning of the contrast agent injection. The main goal is to assess distant spread, notably to the liver and/or peritoneum.

Conventional CT imaging relies on demonstrating differences in enhancement, with greater enhancement of the normal pancreatic parenchyma compared to the tumor. Several studies suggest that a low-energy acquisition, at 80 kV instead of the usual 120 kV, may improve tumor detection [10, 11]. Dual-energy CT (spectral imaging) is a recently introduced technique that provides images at different energy levels. Recent work strongly suggests that, compared to conventional CT, tumor conspicuity and arterial details are improved by using reconstructed virtual low-energy images [12]. Studies are currently evaluating the potential added benefits of dual-energy CT for assessing locoregional spread.

26.5 Diagnosing the Pancreatic Tumor

The diagnosis of pancreatic tumor relies on the identification of both direct signs, that is, on visualization of the tumor, which is not always possible; and of indirect signs, which reflect the upstream impact of the tumor.

26.5.1 Direct Signs

Over 90% of pancreatic adenocarcinomas are hypoattenuating at the pancreatic arterial phase compared to the adjacent parenchyma and subsequently enhance gradually, either remaining hypoattenuating or becoming isoattenuating and therefore poorly visible at the portal phase (Fig. 26.1). The tumor contours are often ill-defined. Large tumors may alter the contours of the pancreatic gland.

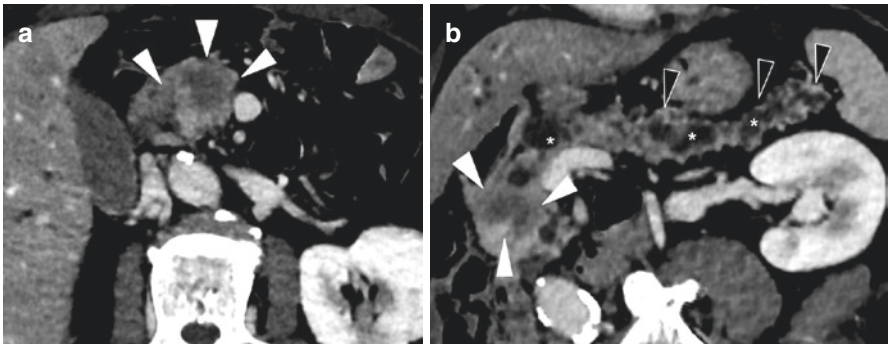

Fig. 26.1 Direct CT signs of pancreatic adenocarcinoma. CT with contrast injection at the pancreatic arterial phase, axial views (**a** and **b**) showing a hypoattenuating mass in the pancreatic head (white arrowheads) with parenchymal atrophy (black arrowheads) and upstream dilation of the main pancreatic duct (asterisks)

Isoattenuating tumors contribute to about 5–10% of cancers. These tumors are not directly visible and can be identified or suspected only based on indirect signs. MRI of the pancreas is indicated in this situation as a complementary investigation to provide further details on the lesion.

26.5.2 Indirect Signs

The indirect signs are seen upstream of the tumor and may vary according to the tumor site (Fig. 26.2). The following descriptions may occur at all sites in the gland, while dilatation of the bile duct is usually associated with locations in the head of pancreas.

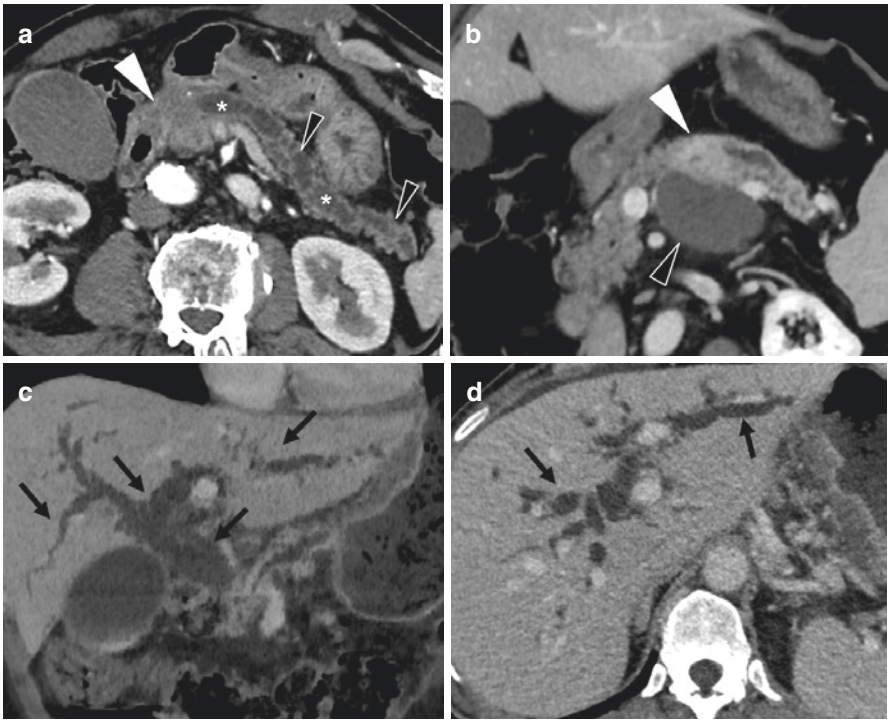

Fig. 26.2 Indirect CT signs of pancreatic adenocarcinoma. CT with contrast injection, axial views (**a** and **d**), coronal view (**b**), and coronal reconstruction with MinIP (**c**) showing the various indirect signs of pancreatic adenocarcinoma: Dilation of the main pancreatic duct (asterisks) and parenchymal atrophy (black arrowheads) upstream from a tumor in the pancreatic isthmus (white arrowhead) (**a**). Dilation of the intrahepatic and extrahepatic bile ducts (black arrows) upstream from a tumor in the pancreatic head (**c** and **d**). Retentive pseudocyst (black arrowhead) upstream from an isoattenuating tumor in the pancreatic head (white arrowhead) (**b**)

26.5.2.1 Pancreatic Duct Dilation

Tumors in the head are more likely than those in the body of the pancreas to cause dilation of the main pancreatic duct. The dilation occurs upstream of an obstruction of the duct by the tumor. Dilation is defined as a main pancreatic duct diameter greater than 3 mm, which usually ends abruptly at the site of the tumor. The secondary ducts may also undergo dilation, which is easier to identify by magnetic resonance cholangiopancreatography.

26.5.2.2 Parenchymal Atrophy

Atrophy of the pancreatic parenchyma is also a consequence of duct obstruction and is therefore often seen in combination with duct dilation. Atrophy indicates chronic obstructive pancreatitis.

26.5.2.3 Retention Pseudocyst

Retention pseudocysts are seen in less than 10% of patients with pancreatic cancer. The mechanism is either rupture of a dilated secondary duct or upstream obstructive pancreatitis. Multiple pseudocysts may be present in the same patient. CT shows peripancreatic structures that are located upstream from the tumor, exhibit fluid attenuation, and are usually devoid of a wall. Pseudocysts are a common source of diagnostic errors.

26.5.2.4 Bile Duct Dilation

For tumors in the head of the pancreas, dilation of the main bile duct and intrahepatic bile ducts is a very common. Retentive hydrops of the gallbladder is frequently seen, as the obstruction is usually located under the level of the cystic duct. The combination of bile duct dilation and main pancreatic duct dilation is known as the double-duct sign and, even when no other signs are present, is strongly suggestive of a cephalic pancreatic tumor.

26.5.3 Diagnostic Performance

The performance of CT for diagnosing the presence of pancreatic adenocarcinoma is excellent, with diagnostic accuracy reported at about 89% [13]. Sensitivity and specificity have ranged from 78% to 96.8% [13–18] and from 98.3% to 100% [13, 14, 19], respectively. Mass-forming chronic pancreatitis is the main differential diagnosis and may be mistaken for a pancreatic tumor.

26.6 Staging Workup

CT provides information on both locoregional spread and metastatic spread. The locoregional evaluation includes vascular assessment of veins and arteries, the retroportal pancreatic tissue, perineural and duodenal and nodal involvement. Distant spread concerns mainly the liver, lungs and peritoneum.

26.6.1 Vascular Spread

An accurate assessment of vascular spread is a crucial component of the staging workup, as its results govern the potential for surgical resection. The resection margins are usually thinnest in contact with the blood vessels. Imaging therefore plays a key role in predicting vascular spread and determining whether tumor-free resection margins (R0) will be achievable. An essential point is performance of the imaging assessment before any therapeutic procedures and, more specifically, before endoscopic ultrasound with aspiration or bile duct stenting. These procedures can induce tissue remodeling with, in the mildest forms, infiltration or peripancreatic and mesenteric fat stranding, which may result in overestimation of vascular spread.

CT has good diagnostic performance for predicting vascular spread, with sensitivities ranging from 70% to 96% and specificities from 82% to 100% [20–22]. In addition, the false-positive rate is low, as established by two recent metaanalyses [23, 24]. This last point is crucial, as false-positive findings may lead to an inappropriate decision not to perform surgery, thereby resulting in loss of chance for the patient. Diagnostic performance is dependent upon performance in detecting the tumor, as vascular abutment that is contiguous with the pancreatic lesion has good specificity for diagnosing tumor spread. An important step is therefore careful examination of the dedicated pancreatic arterial phase images acquired using a multidetector CT machine, as described above.

The performance characteristics of MRI of the pancreas are similar overall to those of CT [25–28]. CT is the reference standard investigation, however, as it is more widely available, more reproducible, and offers better spatial resolution.

Several classifications of vascular spread are available. The most widely used is the one developed by the NCCN, which distinguishes resectable lesions, borderline-resectable lesions, and locally advanced lesions.

26.6.2 Venous Spread

Signs of venous spread listed from the most to the least specific are as follows: obstruction or thrombosis of the vein, vessel caliber irregularity or stenosis, and focal tethering of the vein to the tumor (teardrop sign). Contact of the tumor with the vein along less than 180° of the vein circumference, without stenosis, is not specific of tumor spread. Tumor contact along more than 180° of the vein

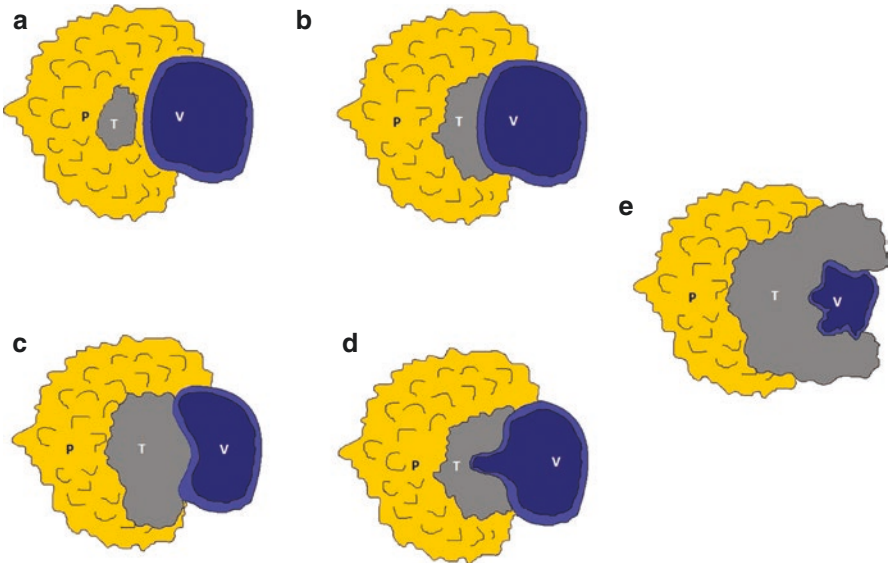

Fig. 26.3 Diagram of venous spread. (**a**) No venous spread, (**b**) contact <180° with no stenosis, (**c**) contact <180° with stenosis, (**d**) teardrop sign, (**e**) venous encasement >180°. *P* pancreas, *T* tumor, *V* vein

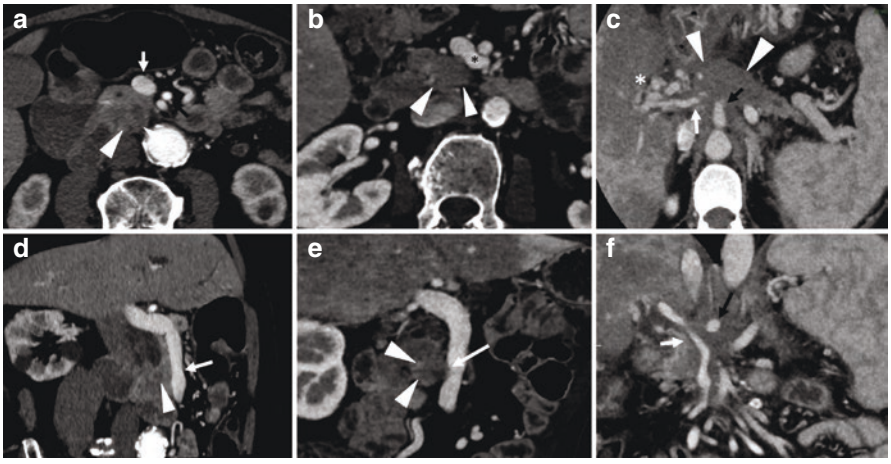

Fig. 26.4 Example of CT images showing venous invasion by the tumor. CT with contrast injection at the pancreatic arterial phase, axial (**b**) and coronal (**a**, **c**, and **d**) views showing several lesions in the pancreatic head (white arrowheads) with different types of venous involvement (black arrowheads): (**a**) contact <180° with the superior mesenteric vein, with no stenosis, (**b**) contact <180° with the superior mesenteric vein, with stenosis, (**c**) contact <180° with the superior mesenteric vein, with a teardrop sign (**e**), (**f**) encasement of the superior mesenteric vein >180°, with stenosis

circumference with no deformity or stenosis of the vein is exceedingly rare. Figure 26.3 illustrate different types of venous spread and Fig. 26.4 shows some examples. The criteria for venous spread used in the NCCN classification [2] is presented in Box 26.2.

Box 26.2 Venous Spread According to NCCN Criteria

- A resectable tumor has no tumor contact with the superior mesenteric vein or portal vein or ≤180° contact without vein contour irregularity.
- A borderline-resectable tumor has >180° solid tumor contact with the superior mesenteric vein or portal vein, or ≤180° contact with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.
- A locally advanced tumor is defined as an unreconstructible superior mesenteric/portal vein due to tumor involvement or occlusion (can be due to tumor or bland thrombus) or, contact with the most proximal draining jejunal branch into the superior mesenteric vein.

26.6.3 Arterial Spread

Arterial encasement by the tumor along more than 180° of the artery circumference is highly specific of tumor spread. The pretreatment workup should carefully assess the celiac axis, common hepatic artery, and superior mesenteric artery. Spread to the common hepatic artery may predict poor survival [29]. The criteria for arterial spread is shown in Box 26.3. Figures 26.5 and 26.6 illustrate different types of arterial involvement.

In addition to the criteria for tumor spread, the following must be routinely assessed as part of the arterial workup:

- Presence of an arcuate ligament causing stenosis of the celiac axis.
- Presence of an aberrant right hepatic artery (defined as arising from the superior mesenteric artery).

An aberrant or misplaced right hepatic artery may travel within the retroportal pancreatic lamina if it arises from the proximal superior mesenteric artery. When not appropriately identified, a misplaced right hepatic artery in the retroportal pancreatic lamina may be injured during pancreatoduodenectomy, leading to a risk of bile duct ischemia if it is the sole hepatic artery supplying the entire liver.

Recent studies have established that the presence of a right hepatic artery has no influence on the cancer prognosis. However, although a right hepatic artery is no longer viewed as an absolute contraindication to pancreatoduodenectomy, the risk of leakage at the bile duct-intestinal tract anastomosis is increased. Routine embolization 3 weeks before surgery has been suggested as a means of developing collateral arteries and thus diminishing the risk of complications related to the resection [30].

Figure 26.7 illustrate some examples of a resectable, a borderline resectable and not locally advanced tumor in CT.

Box 26.3 Artertial Spread According to NCCN Criteria

- A resectable tumor has no tumor contact with the celiac axis, superior mesenteric artery, or common hepatic artery.
- The criteria for borderline-resectable tumors depend on the location of the tumor:
  - *Pancreatic head/uncinate process*: solid tumor contact with the common hepatic artery, without extension to the celiac axis or hepatic artery bifurcation, or solid tumor contact with the superior mesenteric artery along ≤180°.
  - *Pancreatic body/tail*: solid tumor contact with the celiac axis along ≤180°. Note that some groups include in the borderline-resectable category a solid tumor contact with the celiac axis along >180° without involvement of the aorta and with an intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure.
- A locally advanced tumor has solid tumor contact >180° with the celiac axis, contact with the common hepatic artery with extension to the bifurcation or celiac axis, and contact >180° with the superior mesenteric artery or contact with the first jejunal branch or aorta.

26.6.4 Retroportal Pancreatic Lamina

The retroportal pancreatic lamina is a triangular retroperitoneal space between the pancreatic parenchyma and the right edge of the superior mesenteric artery. Figure 26.8 illustrate this retroportal pancreatic lamina in CT. It contains fatty tissue, blood vessels (the superior and inferior pancreaticoduodenal arteries and veins), and lymphatic vessels [31] and is therefore a pathway for malignant cell dissemination from tumors in the pancreatic head.

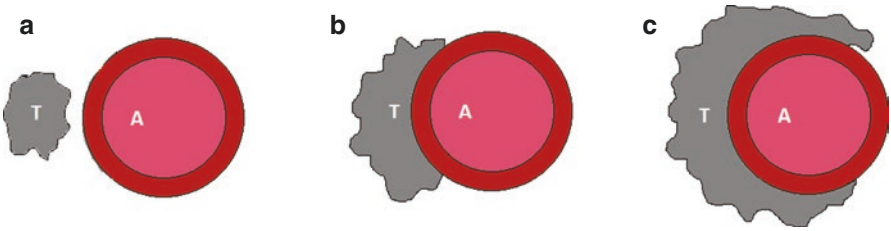

Fig. 26.5 Diagram of arterial spread. (**a**) No arterial spread, (**b**) arterial contact <180°, (**c**) arterial contact >180°, with or without caliber irregularity

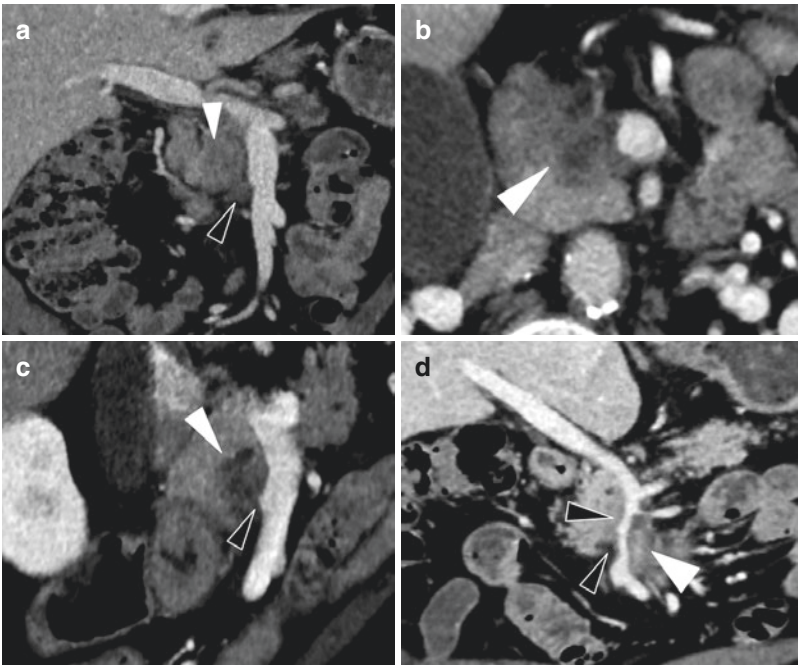

Fig. 26.6 Example of CT images showing arterial invasion by the tumor. CT with contrast injection at the pancreatic arterial phase, axial (**a**, **c**, and **e**) and coronal (**b**, **d**, and **f**) views showing different types of arterial involvement: (**a** and **b**) no arterial involvement by a tumor in the distal femoral head (white arrowheads), at a distance from the superior mesenteric artery. (**c** and **d**) Arterial contact <180° with no change in arterial caliber; tumor in the head of the pancreas (white arrowheads) with focal contact with the origin of the common hepatic artery (white arrows) circumferential arterial encasement of the superior mesenteric artery (black arrows) by a hypoattenuating tumor in the lower part of the pancreatic head

The retroportal pancreatic lamina is among the most common sites of residual tumor after incomplete resection [32]. Identifying spread to the retroportal space during the imaging workup is therefore crucial to guide the surgical strategy. Unequivocal involvement of the retroportal pancreatic space, even without vascular involvement, classifies the tumor as borderline-resectable and warrants neoadjuvant chemotherapy to maximize the likelihood of achieving R0 resection.

On CT-imaging, involvement of the retroportal pancreatic lamina is defined as low-attenuation infiltration of the fatty tissue that has the same attenuation value as, and is contiguous with, the tumor. Few studies have focused specifically on the diagnostic performance of CT for detecting retroportal pancreatic lamina involvement. In a recent study, sensitivity was 60%, specificity 100%, the negative predictive value 81%, and the positive predictive value 100% [33].

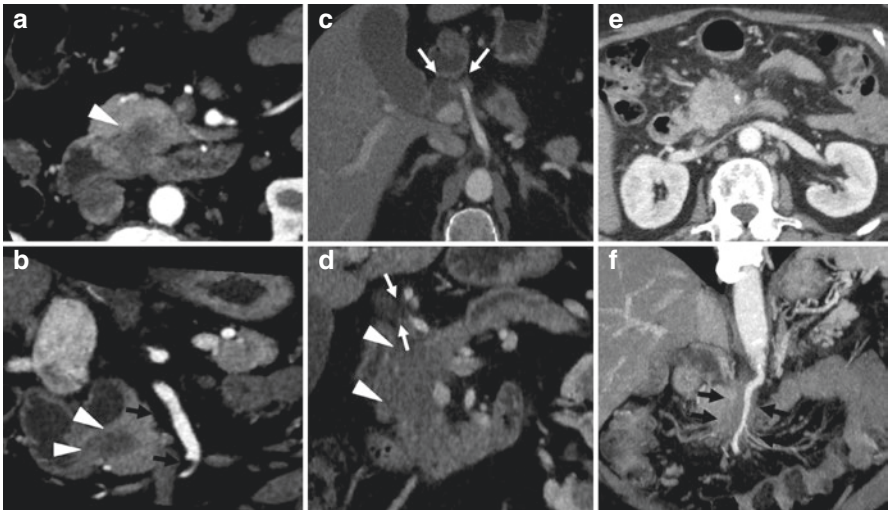

Fig. 26.7 Illustration of locoregional staging by CT. CT with contrast injection at the pancreatic arterial phase, axial (**a**, **c**, and **e**) and coronal (**b**, **d**, and **f**) views. (**a** and **b**) **Resectable tumor** in the head of the pancreas (white arrowhead) that has no contact with the superior mesenteric vein (white arrow), no alterations in caliber, and no contact with the superior mesenteric artery (black arrow). (**c** and **d**) **Borderline-resectable tumor** in the head of the pancreas (white arrowheads) that has <180° contact with the right edge of the superior mesenteric vein but also exhibits a focal stenosis opposite the contact site (white arrows), as well as contact with the end of the first jejunal branch (black asterisk). There is no arterial contact. (**e** and **f**) **Locally advanced tumor** seen as an infiltrating hypoattenuating mass in the isthmus (white arrowhead), with circumferential encasement of the main portal vein and superior mesenteric vein (white arrow) responsible for near-complete occlusion with a portal cavernoma (white asterisk). Note also the circumferential encasement of the celiac axis (black arrow)

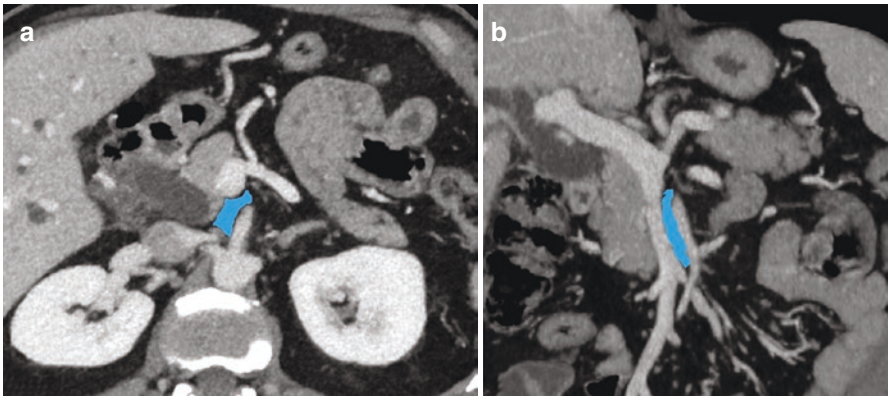

Fig. 26.8 Retroportal pancreatic lamina**.** CT with contrast injection at the portal venous phase, axial (**a**) and coronal (**b**) view. Retroportal pancreatic lamina is illustrated by the blue shape

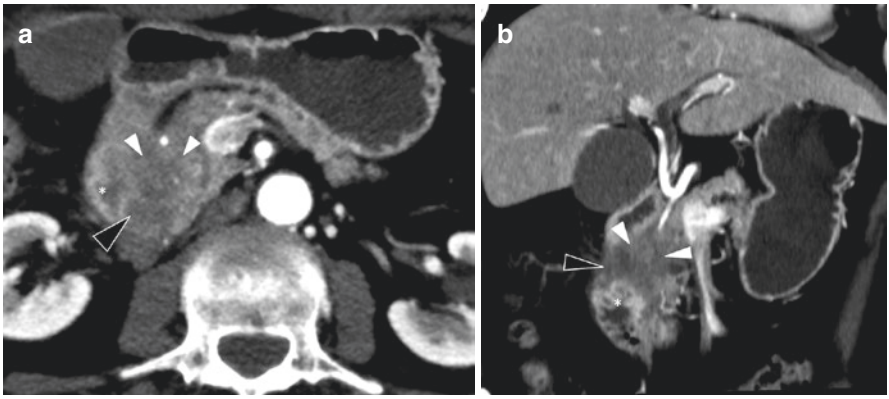

Fig. 26.9 CT signs of duodenal involvement. CT with contrast injection at the pancreatic arterial phase, axial (**a**) view and coronal reconstruction (**b**): large tumor in the head of the pancreas (white arrows) with invasion of the wall of the second part of the duodenum (the black arrows indicate tumor spread and the asterisk the duodenum)

26.6.5 Perineural and Periduodenal Spread

In a recent study, signs on CT of extrapancreatic perineural spread or of duodenal spread was associated with poorer survival after pancreatoduodenectomy [34]. Perineural spread is defined on CT images as hypoattenuating infiltration of the fatty tissue extending directly from the tumor along the perineural extension pathways of the tumor. The main nerve plexuses that supply the cephalic region and uncinate process are the plexus pancreaticus capitalis I and II, the celiac plexuses, the plexuses of the superior mesenteric artery, the plexus of the gastroduodenal artery, and the plexus of the common hepatic artery [35].

The CT definition of duodenal involvement is hypoattenuating infiltration of the duodenal wall, with or without regular or nodular wall thickening, contiguous with the pancreatic tumor [36]. Figure 26.9 shows an example of periduodenal spread.

26.6.6 Lymph Node Involvement

Lymph node involvement is associated with poorer survival in patients with resectable pancreatic carcinoma [29, 37]. The performance of CT for predicting lymph node involvement is very poor [38], with recent studies showing ranges of 38–77% for diagnostic accuracy, 14–24% for sensitivity, and 85–88% for specificity [39, 40]. The classical criterion used to diagnose nodal involvement on CT images is visualization of a peritumoral lymph node whose shortest dimension exceeds 10 cm. However, node enlargement to more than 10 mm is often due to inflammation alone, and, on the other hand, nodes involved by the malignancy may measure less than 10 mm. Other criteria are an ovoid shape, loss of the fatty hilum, and node clustering, but none of these seems to reliably predict malignancy [39]. Finally, CT has

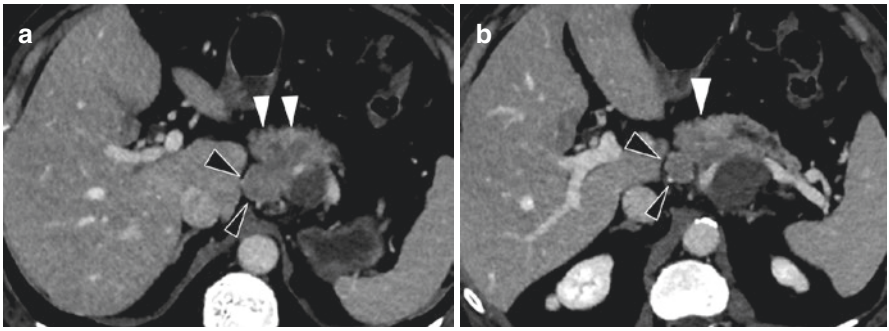

Fig. 26.10 Nodal involvement. CT with contrast injection at the portal venous phase, axial views (**a** and **b**). Tissue mass in the pancreatic body and isthmus (white arrows), with upstream dilation of the pancreatic duct. Two enlarged peritumoral celiac nodes with abnormal features (rounded shape, smallest dimension longer than 10 mm)

only fair sensitivity for detecting distant involved nodes, notably in the retroperitoneal space (Fig. 26.10).

Endoscopic ultrasound may perform better than CT for predicting nodal involvement, despite having only fair sensitivity and specificity. Agreement between CT and endoscopic ultrasound is moderate overall, with a kappa value of 0.54 in one study [41].

Positron emission tomography (PET)/CT may be indicated when the diagnosis is in doubt. However, the limited spatial resolution of this technique results in low sensitivity, of only 42% in one study [42].

In practice, the identification by CT of one or more peripancreatic nodes measuring more than 10 mm does not contraindicate surgery provided the criteria for resectability are met [43, 44]. In contrast, a positive node for CT invasion that is located at a distance from the pancreatic tumor (notably in the lumbo-aortic chain) may be a contraindication to surgical treatment. The nodes must be identified and described in the imaging study report as a map to guide initial node sampling before or during surgery.

Several new techniques currently in development could improve the diagnostic performance of imaging for predicting nodal spread. Especially, analyzing CT radiomics data may hold promise, although further studies are needed to evaluate this method and make it suitable for use in everyday practice [45].

26.7 Evaluation of Distant Spread

Over 50% of patients with pancreatic adenocarcinoma have metastatic disease at the time of the diagnosis [46]. The two most common sites of metastases are the liver and peritoneum. Metastases at other sites such as the lungs and bone are less common and develop later in the course of the disease.

Liver metastases from pancreatic adenocarcinoma are usually seen as small and ill-defined foci of low attenuation. The diagnostic performance of CT for detecting liver metastases is only fair [41–44], with 69% sensitivity compared to 85% by MRI [45]. The main risk is failure to detect small liver metastases, whose presence contraindicates surgical treatment. MRI performs better than CT for detecting liver metastases [5, 47], notably with diffusion imaging, which is 87.5% sensitive and 85.3% specific. Diffusion MRI has been reported to detect liver metastases in about 10% of patients whose liver appears normal by CT [6]. A recent meta-analysis also conclude that MRI has a significant higher sensitivity than CT for detection of liver metastasis [48].

Consequently, MRI of the liver must be performed routinely as part of the preoperative staging workup in patients with pancreatic adenocarcinoma classified as resectable based on the CT findings [49].

Peritoneal metastases are seen by CT as nodular foci of high attenuation in the peripheral fatty tissue; irregular and micronodular thickening of the peritoneal leaflets; fluid within the peritoneal cavity, with or without septation; and nodules of peritoneal tissue. The diagnostic performance of CT for detecting peritoneal involvement is only moderate and has usually been evaluated simultaneously with performance in detecting liver metastases. Here also, diffusion MRI is a more sensitive method of detecting peritoneal lesions.

26.8 Conclusion

Imaging is a pivotal component of the initial workup for pancreatic adenocarcinoma. CT is performed routinely, both to establish the diagnosis and to assess tumor spread to locoregional structures (notably blood vessels) and distant sites. MRI is indicated when an isoattenuating tumor is suspected and is performed routinely as part of the preoperative workup in order to rule out liver metastases.

References

1. Seufferlein T, Bachet JB, Van Cutsem E, Rougier P, on behalf of the ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl 7):vii33–40.
2. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, Version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(8):1028–61.
3. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006;13(8):1035–46.
4. Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(20):2324–8.

5. Motosugi U, Ichikawa T, Morisaka H, Sou H, Muhi A, Kimura K, et al. Detection of pancreatic carcinoma and liver metastases with Gadoxetic acid–enhanced MR imaging: comparison with contrast-enhanced multi–detector row CT. Radiology. 2011;260(2):446–53.
6. Marion-Audibert A-M, Vullierme M-P, Ronot M, Mabrut J-Y, Sauvanet A, Zins M, et al. Routine MRI with DWI sequences to detect liver metastases in patients with potentially resectable pancreatic ductal carcinoma and normal liver CT: a prospective multicenter study. AJR Am J Roentgenol. 2018;211(5):W217–25.
7. Tamm EP, Balachandran A, Bhosale PR, Katz MH, Fleming JB, Lee JH, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin N Am. 2012;50(3):407–28.
8. Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology. 2014;270(1):248–60.
9. Zins M, Matos C, Cassinotto C. Pancreatic adenocarcinoma staging in the era of preoperative chemotherapy and radiation therapy. Radiology. 2018;287(2):374–90.
10. Patel BN, Thomas JV, Lockhart ME, Berland LL, Morgan DE. Single-source dual-energy spectral multidetector CT of pancreatic adenocarcinoma: optimization of energy level viewing significantly increases lesion contrast. Clin Radiol. 2013;68(2):148–54.
11. Macari M, Spieler B, Kim D, Graser A, Megibow AJ, Babb J, et al. Dual-source dual-energy MDCT of pancreatic adenocarcinoma: initial observations with data generated at 80 kVp and at simulated weighted-average 120 kVp. Am J Roentgenol. 2010;194(1):W27–32.
12. Nagayama Y, Tanoue S, Inoue T, Oda S, Nakaura T, Utsunomiya D, et al. Dual-layer spectral CT improves image quality of multiphasic pancreas CT in patients with pancreatic ductal adenocarcinoma. Eur Radiol. 2019;30(1):394–403.
13. Toft J, Hadden WJ, Laurence JM, Lam V, Yuen L, Janssen A, et al. Imaging modalities in the diagnosis of pancreatic adenocarcinoma: a systematic review and meta-analysis of sensitivity, specificity and diagnostic accuracy. Eur J Radiol. 2017;92:17–23.
14. Yamada Y, Mori H, Matsumoto S, Kiyosue H, Hori Y, Hongo N. Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. Abdom Imaging. 2010;35(2):163–71.
15. Kauhanen SP, Komar G, Seppänen MP, Dean KI, Minn HR, Kajander SA, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg. 2009;250(6):957–63.
16. Mehmet Erturk S, Ichikawa T, Sou H, Saitou R, Tsukamoto T, Motosugi U, et al. Pancreatic adenocarcinoma: MDCT versus MRI in the detection and assessment of locoregional extension. J Comput Assist Tomogr. 2006;30(4):583–90.
17. Park MJ, Kim YK, Choi S, Rhim H, Lee WJ, Choi D. Preoperative detection of small pancreatic carcinoma: value of adding diffusion-weighted imaging to conventional MR imaging for improving confidence level. Radiology. 2014;273(2):433–43.
18. Rao S-X, Zeng M-S, Cheng W-Z, Yao X-Z, Jin D-Y, Ji Y. Small solid tumors (< or = 2 cm) of the pancreas: relative accuracy and differentiation of CT and MR imaging. Hepato-Gastroenterology. 2011;58(107–108):996–1001.
19. Gangi S, Fletcher JG, Nathan MA, Christensen JA, Harmsen WS, Crownhart BS, et al. Time interval between abnormalities seen on CT and the clinical diagnosis of pancreatic cancer: retrospective review of CT scans obtained before diagnosis. AJR Am J Roentgenol. 2004;182(4):897–903.
20. Fletcher JG, Wiersema MJ, Farrell MA, Fidler JL, Burgart LJ, Koyama T, et al. Pancreatic malignancy: value of arterial, pancreatic, and hepatic phase imaging with multi-detector row CT. Radiology. 2003;229(1):81–90.
21. Catalano C, Laghi A, Fraioli F, Pediconi F, Napoli A, Danti M, et al. Pancreatic carcinoma: the role of high-resolution multislice spiral CT in the diagnosis and assessment of resectability. Eur Radiol. 2003;13(1):149–56.

22. Karmazanovsky G, Fedorov V, Kubyshkin V, Kotchatkov A. Pancreatic head cancer: accuracy of CT in determination of resectability. Abdom Imaging. 2005;30(4):488–500.
23. Yang R, Lu M, Qian X, Chen J, Li L, Wang J, et al. Diagnostic accuracy of EUS and CT of vascular invasion in pancreatic cancer: a systematic review. J Cancer Res Clin Oncol. 2014;140(12):2077–86.
24. Zhao W-Y, Luo M, Sun Y-W, Xu Q, Chen W, Zhao G, et al. Computed tomography in diagnosing vascular invasion in pancreatic and periampullary cancers: a systematic review and meta-analysis. Hepatobiliary Pancreat Dis Int. 2009;8(5):457–64.
25. Koelblinger C, Ba-Ssalamah A, Goetzinger P, Puchner S, Weber M, Sahora K, et al. Gadobenate Dimeglumine–enhanced 3.0-T MR imaging versus multiphasic 64–detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. Radiology. 2011;259(3):757–66.
26. Park HS, Lee JM, Choi HK, Hong SH, Han JK, Choi BI. Preoperative evaluation of pancreatic cancer: comparison of gadolinium-enhanced dynamic MRI with MR cholangiopancreatography versus MDCT. J Magn Reson Imaging. 2009;30(3):586–95.
27. Chen F-M, Ni J-M, Zhang Z-Y, Zhang L, Li B, Jiang C-J. Presurgical evaluation of pancreatic cancer: a comprehensive imaging comparison of CT versus MRI. AJR Am J Roentgenol. 2016;206(3):526–35.
28. Treadwell JR, Zafar HM, Mitchell MD, Tipton K, Teitelbaum U, Jue J. Imaging tests for the diagnosis and staging of pancreatic adenocarcinoma: a meta-analysis. Pancreas. 2016;45(6):789–95.
29. Bae JS, Kim JH, Joo I, Chang W, Han JK. MDCT findings predicting post-operative residual tumor and survival in patients with pancreatic cancer. Eur Radiol. 2019;29(7):3714–24.
30. El Amrani M, Pruvot F-R, Truant S. Management of the right hepatic artery in pancreaticoduodenectomy: a systematic review. J Gastrointest Oncol. 2016;7(2):298–305.
31. Bouassida M, Mighri MM, Chtourou MF, Sassi S, Touinsi H, Hajji H, et al. Retroportal lamina or mesopancreas? Lessons learned by anatomical and histological study of thirty three cadaveric dissections. Int J Surg. 2013;11(9):834–6.
32. Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, et al. Practical usefulness of lymphatic and connective tissue clearance for the carcinoma of the pancreas head. Ann Surg. 1988;208(2):215–20.
33. Bonello L, Monfardini L, Bnà C, Villanacci A, Bonaventure T, Savio A, et al. Diagnostic accuracy of CT in predicting retroportal lamina infiltration in patients with pancreatic cancer [Internet]. 2017 [cited 2019 Oct 15]. Available from: https://posterng.netkey.at/esr/viewing/index.php?module=viewing_poster&task=viewsection&pi=139600&ti=479966&si=1643&searchkey=#poster
34. Chang ST, Jeffrey RB, Patel BN, DiMaio MA, Rosenberg J, Willmann JK, et al. Preoperative multidetector CT diagnosis of extrapancreatic perineural or duodenal invasion is associated with reduced postoperative survival after pancreaticoduodenectomy for pancreatic adenocarcinoma: preliminary experience and implications for patient care. Radiology. 2016;281(3):816–25.
35. Zuo H-D, Zhang X-M, Li C-J, Cai C-P, Zhao Q-H, Xie X-G, et al. CT and MR imaging patterns for pancreatic carcinoma invading the extrapancreatic neural plexus (Part I): Anatomy, imaging of the extrapancreatic nerve. World J Radiol. 2012;4(2):36–43.
36. Padilla-Thornton AE, Willmann JK, Jeffrey RB. Adenocarcinoma of the uncinate process of the pancreas: MDCT patterns of local invasion and clinical features at presentation. Eur Radiol. 2012;22(5):1067–74.
37. Tol JAMG, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
38. Tseng DSJ, van Santvoort HC, Fegrachi S, Besselink MG, Zuithoff NPA, Borel Rinkes IH, et al. Diagnostic accuracy of CT in assessing extra-regional lymphadenopathy in pan-

creatic and peri-ampullary cancer: a systematic review and meta-analysis. Surg Oncol. 2014;23(4):229–35.
39. Roche CJ, Hughes ML, Garvey CJ, Campbell F, White DA, Jones L, et al. CT and pathologic assessment of prospective nodal staging in patients with ductal adenocarcinoma of the head of the pancreas. AJR Am J Roentgenol. 2003;180(2):475–80.
40. Nawaz H, Fan CY, Kloke J, Khalid A, McGrath K, Landsittel D, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP. 2013;14(5):484–97.
41. Du T, Bill KA, Ford J, Barawi M, Hayward RD, Alame A, et al. The diagnosis and staging of pancreatic cancer: a comparison of endoscopic ultrasound and computed tomography with pancreas protocol. Am J Surg. 2018;215(3):472–5.
42. Asagi A, Ohta K, Nasu J, Tanada M, Nadano S, Nishimura R, et al. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. Pancreas. 2013;42(1):11–9.
43. Moutardier V, Giovannini M, Magnin V, Viret F, Lelong B, Delpero J-R. How to improve treatment of resectable pancreatic adenocarcinomas? Surgical resection, histopathological examination, adjuvant therapies. Gastroenterol Clin Biol. 2004;28(11):1083–91.
44. Imai H, Doi R, Kanazawa H, Kamo N, Koizumi M, Masui T, et al. Preoperative assessment of para-aortic lymph node metastasis in patients with pancreatic cancer. Int J Clin Oncol. 2010;15(3):294–300.
45. Bian Y, Guo S, Jiang H, Gao S, Shao C, Cao K, et al. Relationship between radiomics and risk of lymph node metastasis in pancreatic ductal adenocarcinoma. Pancreas. 2019;48(9):1195–203.
46. Golan T, Sella T, Margalit O, Amit U, Halpern N, Aderka D, et al. Short- and long-term survival in metastatic pancreatic adenocarcinoma, 1993–2013. J Natl Compr Cancer Netw. 2017;15(8):1022–7.
47. Jeon SK, Lee JM, Joo I, Lee DH, Ahn SJ, Woo H, et al. Magnetic resonance with diffusion-weighted imaging improves assessment of focal liver lesions in patients with potentially resectable pancreatic cancer on CT. Eur Radiol. 2018;28(8):3484–93.
48. Alabousi M, McInnes MD, Salameh J-P, Satkunasingham J, Kagoma YK, Ruo L, et al. MRI vs. CT for the detection of liver metastases in patients with pancreatic carcinoma: a comparative diagnostic test accuracy systematic review and meta-analysis. J Magn Reson Imaging. 2020; https://doi.org/10.1002/jmri.27056.
49. Kim HW, Lee J-C, Paik K-H, Kang J, Kim YH, Yoon Y-S, et al. Adjunctive role of preoperative liver magnetic resonance imaging for potentially resectable pancreatic cancer. Surgery. 2017;161(6):1579–87.

Chapter 27
MR/MRCP for Diagnosis and Staging

Xavier Merino-Casabiel and C. Ortiz-Andrade

Take Home Messages

- On MRI, pancreatic adenocarcinoma typically appears as an ill-defined, hypointense solid mass on fat-suppressed T1-weighted images and on the pancreatic parenchymal phase of dynamic gadolinium-enhanced fat-suppressed imaging.
- Differential diagnosis of pancreatic adenocarcinoma includes focal chronic pancreatitis, groove pancreatitis, autoimmune pancreatitis, primary pancreatic lymphoma, pancreatic neuroendocrine tumors and metastases to the pancreas.
- The addition of diffusion weighted imaging sequences has been shown to improve the detection of subtle liver metastases in patients with pancreatic adenocarcinoma.

Pearls and Pitfalls

- MRI diagnosis of pancreatic cancer requires an adequate MRI protocol which must include T2-weighted, T1-fat suppressed, dynamic postcontrast T1-fat suppressed, diffusion weighted images and magnetic resonance cholangiopancreatography sequences.
- MRI diagnosis of pancreatic cancer is based in the detection of an ill-defined hypointense and hypovascular mass with or without ancillary signs (common bile duct and/or main pancreatic duct dilatation, upstream pancreatic atrophy, …).
- MRI is increasingly used for detection and characterization of small liver lesions.

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Future Perspectives
- Technical MRI improvements
- Identification of subtle imaging predictors of response to treatment and differentiating viable tumor from posttreatment fibrosis
- Increase the accuracy to detect small liver metastases

27.1 Introduction

Pancreatic cancer is a highly lethal disease, with radical surgical resection as the only curative option. Cross-sectional imaging, specifically multidetector computed tomography (MDCT), plays an essential role in the initial diagnosis and in the staging of pancreatic cancer and is the preferred imaging technique in many institutions given its high availability and reproducibility [1] Over the last years, many technical magnetic resonance imaging (MRI) advances have been made, resulting in improvements in imaging quality and speed of image acquisition. Studies comparing the state-of-the-art MDCT with state-of-the-art MRI report a similar specificity and sensitivity for staging of pancreatic ductal adenocarcinoma [2]. However, MRI is not widely used due to a lack of availability and its higher cost. The actual role of MRI in many medical institutions is as a "problem-solving tool", used in specific situations in which MRI is superior to MDCT, such as in detection of small and/or isoattenuating pancreatic tumors and in characterization of indeterminate hepatic lesions seen on prior MDCT [3–5].

27.2 MRI Protocol for Pancreatic Cancer Evaluation

Although MRI has a limited spatial resolution when compared with MDCT, its major advantage is a very high image contrast without exposing the patient to ionizing radiation. The recommended MRI protocol for a complete evaluation of the pancreas requires a high magnetic field strength scanner (1.5 or 3.0 T main magnetic field) and phased-array multichannel torso coil to achieve high quality images of the gland [6]. All patients fast for at least 4–6 h before the examination. The complete evaluation of the pancreas requires a combination of thin (<6 mm) axial and coronal standard breath-hold morphologic MRI sequences for studying the pancreatic parenchyma: (1) T1-weighted dual-echo; (2) T2-weighted fast spin-echo or single-shot fast spin-echo and (3) T1-weighted fat suppressed (preferable 3D gradient-echo) both unenhanced and dynamic image acquisition after intravenous administration of gadolinium based contrast (dose of 0.1 mmol per kilogram of body weight and with an injection rate of 2 mL/s). Arterial, portal-venous, and equilibrium phase images are obtained approximately at 20–40 s, 45–65 s, and 3–5 min, respectively [7, 8]. In addition, sequences to evaluate the

pancreaticobiliary ductal system [3D or 2D MR cholangiopancreatography (MRCP)] are required (Fig. 27.1).

In addition, diffusion weighted imaging (DWI) is increasingly used as an optional sequence that may improve the detection and characterization of pancreatic focal lesions and the detection of liver and lymph node metastases (Table 27.1) [9].

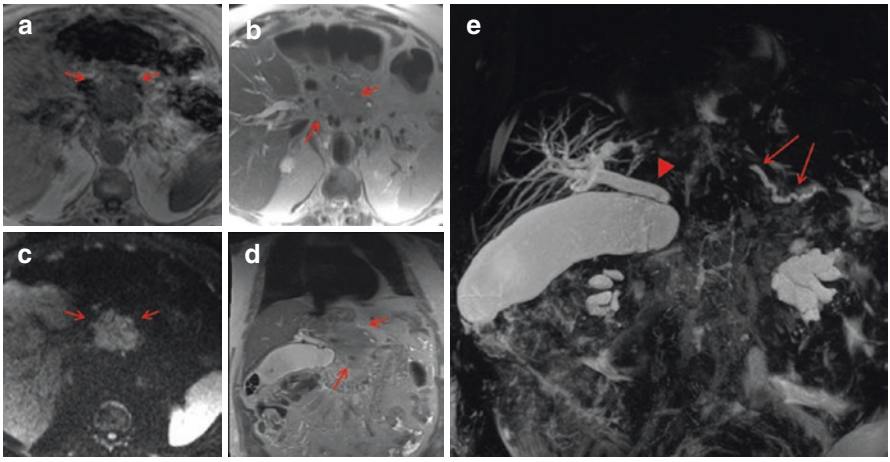

Fig. 27.1 Example of MRI protocol for pancreatic cancer evaluation: Male, 80 year with large non resectable pancreatic adenocarcinoma (short arrows) with bone metastases (not shown): (**a**) Axial T1-weighted, (**b**) Axial T2-weighted single-shot fast spin-echo, (**c**) Axial DWI, (**d**) Coronal T2-weighted single-shot fast spin-echo, and (**e**) Coronal 3D MR cholangiopancreatography (MRCP). Note the "double duct sign": dilatation of the main pancreatic duct (long arrows) and common bile duct (arrowhead)

Table 27.1 Suggested minimum standard pancreatic MRI/MRCP protocol

Sequence	Plane/thickness	Role
2D T2 FSE	Axial and coronal [4–5 mm]	Global anatomy evaluation Pancreaticobiliary ductal anatomy evaluation
2D T2-FS	Axial [5 mm]	Pancreatic mass detection Liver metastases evaluation
3D T2 MRCP	Coronal [1.5 mm]	Pancreaticobiliary ductal anatomy evaluation
Pre-contrast 3D T1-FS	Axial [3 mm]	Pancreatic mass detection
DWI	Axial [5 mm]	Pancreatic mass detection Liver metastases detection
Dynamic post contrast 3D T1-FS (arterial, portal-venous, and equilibrium phases)	Axial [3 mm] (optional: coronal)	Arterial phase: Pancreatic mass detection Portal phase: Lymphadenopathy and liver/peritoneal metastases evaluation.

2D 2-dimensional, *3D* 3-dimensional, *FSE* fast spin echo, *FS* fat suppression

27.3 Typical Pancreatic Cancer Imaging Features

27.3.1 Primary Signs

On MRI, pancreatic adenocarcinoma typically appears as an ill-defined solid mass. It is hypointense in comparison with the adjacent pancreas on fat-suppressed T1-weighted images and during the pancreatic parenchymal phase of dynamic gadolinium-enhanced fat-suppressed imaging. It usually remains hypo-enhancing on the portal venous phase and shows progressive enhancement on delayed sequences [10]. On the other hand, on T2-weighted images, lesions are usually isointense to slightly hyperintense compared with the surrounding pancreatic parenchyma, thereby making it difficult to identify [11]. These MRI features are related to the hypovascular and fibrotic nature of the tumor as opposed to the pancreatic parenchyma [12]. Therefore, small lesions beyond the resolution of CT or iso-attenuating lesions on CT are best detected using unenhanced and early gadolinium-enhanced fat-suppressed T1-weighted images [11]. In the same way, DWI has shown promise for the detection of pancreatic cancer with a high sensitivity and specificity. Lesions typically demonstrate restricted diffusion and therefore appear hyperintense on DWI sequences and hypointense on ADC maps. The high contrast resolution of pancreatic cancer on DWI is useful for the identification of even very small lesions, thus allowing earlier diagnosis (Fig. 27.1) [9, 11, 13].

Most pancreatic adenocarcinomas occur in the head of the pancreas and cause dilatation of both the main pancreatic duct (MPD) and common bile duct (CBD) which is called the “double duct sign” (Fig. 27.1). When the tumor is located in the neck, body or tail, it causes only upstream pancreatic duct dilatation [14, 15]. MRCP images are particularly useful in the assessment for obstruction of the MPD and CBD. Tumors located in the uncinate process may present with no or minimal ductal dilatation, so the uncinate process should always be carefully evaluated to identify the presence of subtle abnormalities [13, 16].

Pancreatic duct obstruction by tumors can lead to pancreatitis in the obstructed gland and the pancreatic parenchyma upstream from the tumor may appear hypointense on T1-weighted images, possibly limiting tumor conspicuity [10].

27.3.2 Secondary Signs

When the primary mass cannot be easily identified, its presence may be inferred by identification of ancillary imaging features. Some of these indirect signs include focal changes of the pancreatic contour, abrupt interruption of the CBD, MPD, or both, with upstream dilatation and atrophy of the parenchyma distal to the lesion [4, 17–19]. Isolated main pancreatic duct dilatation without any visible mass, should be viewed with great suspicion for the possibility of an underlying tumor [20, 21] (Table 27.2).

Table 27.2 Typical pancreatic cancer primary and secondary imaging features

Primary signs	Ill-defined solid mass Hypovascular solid mass
Secondary signs	Focal changes of the pancreatic contour Abrupt interruption and dilatation of the CBP and/or MPD Upstream pancreatic gland atrophy

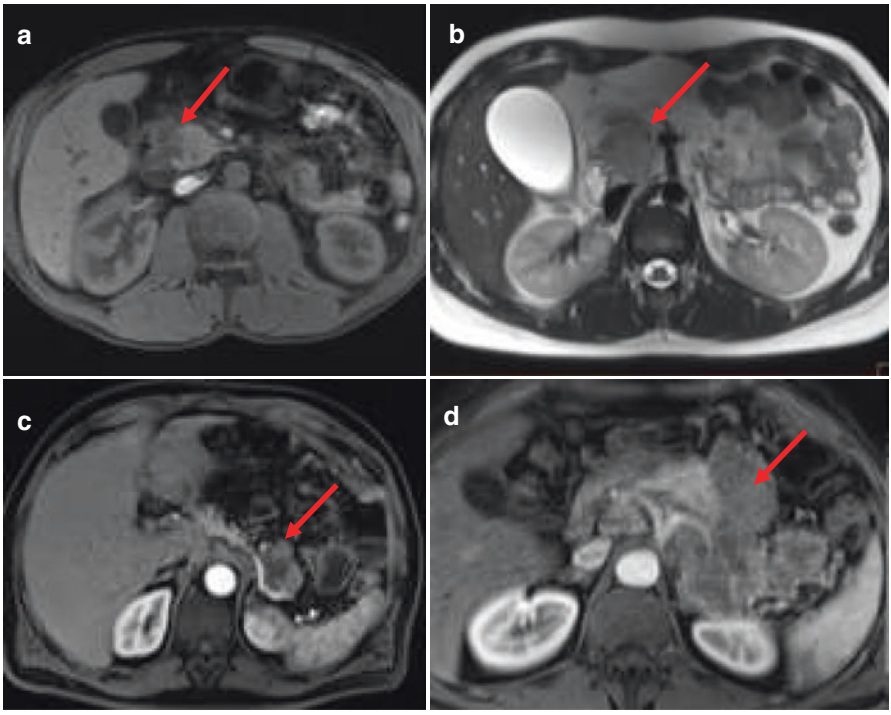

Fig. 27.2 Imaging mimics of pancreatic adenocarcinoma. (**a**) T1-WI with fat suppression: Groove pancreatitis. (**b**) T2-WI: Autoimmune pancreatitis. (**c**) Postcontrast fat-suppressed T1-WI in the arterial phase: Pancreatic hypo-vascular metastases from gastric adenocarcinoma. (**d**) Postcontrast fat-suppressed T1-WI in the arterial phase: p-NET

27.4 Differential Diagnosis

There are some entities that can mimic pancreatic adenocarcinoma (Fig. 27.2) and may lead to diagnostic errors.

Focal chronic pancreatitis can present as a focal inflammatory mass, often located in the pancreatic head causing upstream ductal dilatation, thereby mimicking pancreatic adenocarcinoma [22]. Several findings on MR imaging have been suggested

to aid in the differentiation between the two. Features that favor a diagnosis of focal pancreatitis include a non-obstructed MPD or CBD penetrating the apparent pancreatic mass ("duct penetrating sign") or a smooth tapered narrowing of the pancreatic duct upstream from the pancreatic mass ("icicle sign"), pancreatic duct irregularity, and the presence of pancreatic calcifications [22–24]. Features that favor a diagnosis of pancreatic cancer include an abrupt cutoff of a smoothly dilated pancreatic duct by the mass and upstream pancreatic gland atrophy [15]. DWI may help to distinguish focal chronic pancreatitis from pancreatic adenocarcinoma, since ADC values in an adenocarcinoma are lower than those of the parenchyma, while in chronic pancreatitis, these values are not significantly different from the rest of the gland [9, 22, 25]. However, pancreatic adenocarcinoma can be superimposed on patients with chronic pancreatitis and so, specific findings of chronic pancreatitis may not be sufficient to exclude pancreatic malignancy. Therefore, despite best imaging techniques, biopsy may be necessary for a definitive diagnosis [22].

Pancreatic neuroendocrine tumors (p-NET) can occasionally mimic pancreatic adenocarcinoma when they do not demonstrate the typical arterial enhancement. Some tumors can demonstrate heterogeneous and atypical delayed enhancement which is more often a characteristic associated with pancreatic adenocarcinoma [26]. Features that favor a diagnosis of NET include a well-circumscribed margin, calcifications, vascular infiltration with portal vein tumor thrombus, central necrosis and cystic degeneration. On the other hand, ductal obstruction is uncommon in p-NET [15].

Metastases to the pancreas are relatively rare. Renal cell carcinoma is the most common neoplasm associated with pancreatic metastasis followed by breast carcinoma, lung carcinoma, colorectal carcinoma, and melanoma [27, 28]. The appearances of pancreatic metastases closely resemble that of a primary malignancy [29]. Hypervascular metastases are usually from renal cell carcinoma and their main differential diagnosis is pancreatic NET [30]. On the other hand, hypovascular metastases are usually from lung, breast or colon cancer and the main differential consideration for these lesions is pancreatic adenocarcinoma [15, 22, 31]. Features that favor a diagnosis of metastatic disease include: multiplicity of tumors within the pancreas, absence of ductal dilatation, homogeneous or heterogeneous enhancement, presence of metastases in locations not typically involved in adenocarcinoma of pancreatic origin (such as skeleton or adrenal glands) and typical imaging features of the primary tumor, such as hyperintensity of melanoma at T1-weighted MRI secondary to intratumoral hemorrhage or paramagnetic melanin content [29, 32]. If there is a clinical history of a known extra-pancreatic malignancy, pancreatic metastases should be considered in the differential diagnosis of a pancreatic mass [22].

Groove pancreatitis can mimic pancreatic adenocarcinoma, particularly its segmental form which involves both the pancreaticoduodenal groove and the dorsocranial portion of the pancreatic head, resembling a focal mass in close proximity to

the duodenal wall [33]. The CBD may be narrower in the distal part with mild upstream dilatation and the MPD may be slightly dilated towards the body and tail of the pancreas [33]. Features that favor a diagnosis of groove pancreatitis include its typical location, the thickening of the duodenal wall with multiple small cysts in both the duodenal wall and pancreaticoduodenal groove, a relatively smooth, tapered and regular narrowing of the CBD and a normal or a slightly tapered MPD [34–36]. However, making the distinction between the two entities based only on imaging can be extremely difficult, requiring endoscopy guided biopsy or even pancreaticoduodenectomy (Whipple procedure).

Autoimmune pancreatitis (AIP) is an important mimic of pancreatic carcinoma. Focal disease is less common than diffuse disease and it manifests as a focal mass, often involving the pancreatic head [37]. On MRI, the affected area is usually mildly T2 hyperintense, T1 hypointense with hypo-enhancement on the early postcontrast phase, and delayed hyper-enhancement, an appearance that may mimic that of pancreatic malignancy [22]. Features that favor a diagnosis of autoimmune pancreatitis include an irregular narrowing of the MPD (which is usually longer than the stenosis caused by pancreatic adenocarcinoma) together with the absence of upstream duct dilation, smooth narrowing of the intrapancreatic portion of the CBD without significant upstream dilatation, presence of extra-pancreatic organ involvement (often the biliary system) and elevated IgG4 levels [38].

Primary Pancreatic lymphoma (PPL) is an extremely rare disease representing <0.5% of pancreatic cancers [39]. It may present as a focal mass or diffuse gland enlargement, the former being more common [40]. Focal lymphomatous involvement of the gland is typically restricted to the pancreatic head and can mimic pancreatic adenocarcinoma. PPL presents as a homogeneously T1-hypointense mass, with low to intermediate T2 signal and shows hypo-enhancement compared with the rest of remaining pancreas [11, 40].

Features that favor a diagnosis of lymphoma include a bulky tumor localized in the pancreatic head without significant MPD dilatation (CBD dilatation is more common than MPD dilatation), lymphadenopathy below the level of the renal veins and invasive tumor growth that does not respect anatomic boundaries and encloses the main vascular structures without causing obstruction or occlusion [15, 41].

27.5 Role of MRI in Pancreatic Cancer Imaging

27.5.1 Role of MRI in Local Staging

An accurate preoperative pancreatic cancer staging is crucial to the correct management of the disease. It is important to precisely assess the local extent of the tumor in order to correctly identify patients with resectable disease who are surgical

candidates and differentiate them from those with unresectable disease [11]. Pancreas-specific CT or pancreas-specific MRI have a similar performance in the presurgical evaluation of pancreatic cancer; however, the greater availability of CT may favor its use [17, 42–44]. In those patients who are considered resectable, either of these imaging techniques can also be used in order to facilitate surgical planning [11].

27.5.2 Role of MRI in Extra-Pancreatic Spread Evaluation

Lymph nodes are the most common site for pancreatic carcinoma metastases, followed by the liver [13] Given that more than 50% of all liver metastases develop in the first 6 postoperative months, it is believed that liver metastases are already present at the time of surgery [45]. These small (<1 cm) synchronous liver metastases are usually not detected by routine preoperative MDCT [46]. In this setting, MRI is increasingly used for detection and characterization of small liver lesions, thereby potentially altering patient management (Fig. 27.3). Hepatic metastases are usually hypointense on T1-weighted images and slightly hyperintense on T2-weighted images and are typically hypo-vascular with a ring enhancement pattern after gadolinium contrast administration [47]. The addition of DWI sequences has been shown to improve the sensitivity in the detection of liver metastases in patients with pancreatic tumors [46, 48].

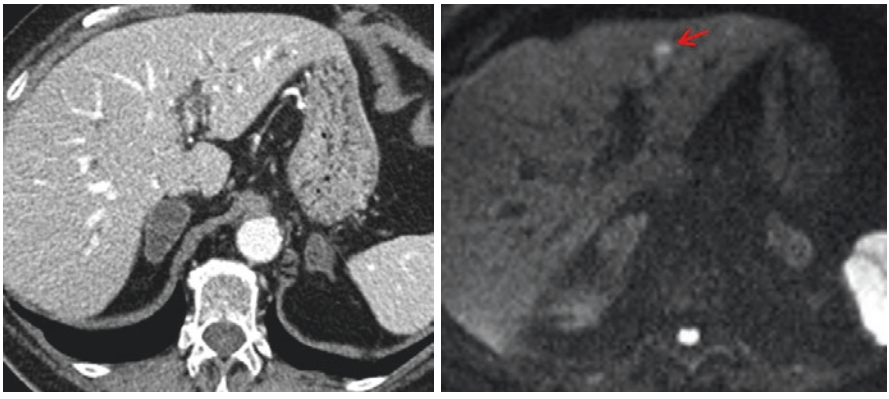

Fig. 27.3 Male. 77 year old with pancreatic carcinoma and subtle liver metastases. Axial liver MDCT scan (left) and MRI–DWI (right) at time of diagnosis. No liver lesions were detected in CT scan, but in the MRI scan (DWI) there was a small liver metastasis in the left liver lobe (arrow)

27.6 Conclusion

Pancreas-specific MRI has a similar performance as pancreas-specific CT in the initial diagnosis and staging of pancreatic cancer. However, the greater availability of CT may favor its use. MRI is specifically used for detection of small and/or isoattenuating pancreatic tumors and in characterization of indeterminate hepatic lesions seen on prior CT, thereby potentially altering patient management.

References

1. Kambadakone AR, Zaheer A, Le O, et al. Multi-institutional survey on imaging practice patterns in pancreatic ductal adenocarcinoma. Abdom Radiol. 2018;43:245–52.
2. Shrikhande SV, Barreto SG, Goel M, Arya S. Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature. HPB (Oxford). 2012;14(10):658–68.
3. NCCN. Guidelines Version 3.2019 Pancreatic Adenocarcinoma. https://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf.
4. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014;20(24):7864–77.
5. Al-Hawary M. Role of imaging in diagnosing and staging pancreatic cancer. J Natl Compr Cancer Netw. 2016;14(5.5):678–80.
6. O'Neill E, Hammond N, Miller FH. MR imaging of the pancreas. Radiol Clin N Am. 2014;52(4):757–77.
7. Kim SW, Yamaue H, editors. Pancreatic cancer with special focus on topical issues and surgical techniques. Berlin: Springer; 2017.
8. Sandrasegaran K, Lin C, Akisik FM, Tann M. State-of-the-art pancreatic MRI. AJR Am J Roentgenol. 2010;195(1):42–53.
9. De Robertis R, Tinazzi Martini P, Demozzi E, Dal Corso F, Bassi C, Pederzoli P, D'Onofrio M. Diffusion-weighted imaging of pancreatic cancer. World J Radiol. 2015;7(10):319–28.
10. Sandrasegaran K, Sahani DV. MR imaging of the pancreas, An issue of magnetic resonance imaging clinics of North America, vol. 26. 3rd ed. Amsterdam: Elsevier Health Sciences; 2018.
11. Healey PR. MRI and MRCP for diagnosis and staging of pancreatic cancer. In: Pancreatic cancer. New York, NY: Springer; 2018. p. 711–34.
12. Deshmukh S, Roth CG. MRI of the pancreaticobiliary system. In: Fundamentals of body MRI. Philadelphia, PA: WB Saunders; 2012. p. 129–97.
13. Jha P, et al. The role of MR imaging in pancreatic cancer. Magn Reson Imag Clin. 2018;26(3):363–73.
14. Yang M-J, et al. Common and unusual CT and MRI manifestations of pancreatic adenocarcinoma: a pictorial review. Quantitat Imag Med Surg. 2013;3(2):113.
15. Low G, et al. Multimodality imaging of neoplastic and nonneoplastic solid lesions of the pancreas. Radiographics. 2011;31(4):993–1015.
16. Chu LC, Goggins MG, Fishman EK. Diagnosis and detection of pancreatic cancer. Cancer J. 2017;23(6):333–42.
17. Chen F-M, et al. Presurgical evaluation of pancreatic cancer: a comprehensive imaging comparison of CT versus MRI. Am J Roentgenol. 2016;206(3):526–35.

18. Prokesch RW, et al. Isoattenuating pancreatic adenocarcinoma at multi–detector row CT: secondary signs. Radiology. 2002;224(3):764–8.
19. Burk KS, et al. Imaging and screening of pancreatic cancer. Radiol Clin. 2017;55(6):1223–34.
20. Kim SW, et al. Isolated main pancreatic duct dilatation: CT differentiation between benign and malignant causes. Am J Roentgenol. 2017;209(5):1046–55.
21. Kim JH, et al. Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. Radiology. 2010;257(1):87–96.
22. Gandhi NS, et al. Imaging mimics of pancreatic ductal adenocarcinoma. Abdom Radiol. 2018;43(2):273–84.
23. Bowman AW, Bolan CW. MRI evaluation of pancreatic ductal adenocarcinoma: diagnosis, mimics, and staging. Abdom Radiol. 2019;44(3):936–49.
24. Ichikawa T, et al. Duct-penetrating sign at MRCP: usefulness for differentiating inflammatory pancreatic mass from pancreatic carcinomas. Radiology. 2001;221(1):107–16.
25. Warda MHA, Hasan DI, Elteeh OA. Differentiation of pancreatic lesions using diffusion-weighted MRI. Egyp J Radiol Nucl Med. 2015;46(3):563–8.
26. Al-Hawary MM, et al. Mimics of pancreatic ductal adenocarcinoma. Cancer Imaging. 2013;13(3):342.
27. Sweeney AD, et al. Value of pancreatic resection for cancer metastatic to the pancreas. J Surg Res. 2010;160(2):268–76.
28. Ahmed S, et al. Metastatic disease to the pancreas: pathologic spectrum and CT patterns. Abdom Imaging. 2013;38(1):144–53.
29. Saba L, Suri JS, editors. Multi-detector CT imaging: abdomen, pelvis, and CAD applications, vol. 2. Boca Raton, FL: CRC Press; 2013.
30. Zaheer A, et al., editors. Pancreatic imaging: a pattern-based approach to radiologic diagnosis with pathologic correlation. New York, NY: Springer; 2017.
31. To'o KJ, et al. Pancreatic and peripancreatic diseases mimicking primary pancreatic neoplasia. Radiographics. 2005;25(4):949–65.
32. Triantopoulou C, et al. Metastatic disease to the pancreas: an imaging challenge. Insights Imag. 2012;3(2):165–72.
33. Triantopoulou C, et al. Groove pancreatitis: a diagnostic challenge. Eur Radiol. 2009;19(7):1736–43.
34. Raman SP, et al. Groove pancreatitis: spectrum of imaging findings and radiology-pathology correlation. Am J Roentgenol. 2013;201(1):W29–39.
35. Tezuka K, et al. Groove pancreatitis. Dig Surg. 2010;27(2):149–52.
36. Pallisera-Lloveras A, et al. Groove pancreatitis. Rev Esp Enferm Dig. 2015;107(5):280–8.
37. Sahani DV, et al. Autoimmune pancreatitis: imaging features. Radiology. 2004;233(2):345–52.
38. Crosara S, et al. Autoimmune pancreatitis: multimodality non-invasive imaging diagnosis. World J Gastroenterol. 2014;20(45):16881.
39. Yu L, Chen Y, Xing L. Primary pancreatic lymphoma: two case reports and a literature review. OncoTargets Ther. 2017;10:1687.
40. Steinman J, et al. Rare pancreatic tumors. Abdom Radiol. 2018;43(2):285–300.
41. Hardacre JM. Pancreatic cancer and periampullary neoplasms, An issue of surgical clinics of North America, vol. 96. 6th ed. Amsterdam: Elsevier Health Sciences; 2016.
42. Lee JK, et al. Prediction of vascular involvement and resectability by multidetector-row CT versus MR imaging with MR angiography in patients who underwent surgery for resection of pancreatic ductal adenocarcinoma. Eur J Radiol. 2010;73(2):310–6.
43. Grenacher L, et al. Diagnosis and staging of pancreatic carcinoma: MRI versus multislice-CT--a prospective study. RoFo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin. 2004;176(11):1624–33.
44. Tamm EP, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin. 2012;50(3):407–28.

45. Riviere DM, van Geenen EJM, van der Kolk BM, Nagtegaal ID, Radema SA, van Laarhoven CJHM, Hermans JJ. Improving preoperative detection of synchronous liver metastases in pancreatic cancer with combined contrast-enhanced and diffusion-weighted MRI. Abdom Radiol. 2019;44(5):1756–65.
46. Holzapfel K, Reiser-Erkan C, Fingerle AA, et al. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. Abdom Imaging. 2011;36:179–84.
47. Danet IM, Semelka RC, Nagase LL, Woosely JT, Leonardou P, Armao D. Liver metastases from pancreatic adenocarcinoma: MR imaging characteristics. J Magn Reson Imaging. 2003;18(2):181–8.
48. Motosugi U, Ichikawa T, Morisaka H, Sou H, Muhi A, Kimura K, et al. Detection of pancreatic carcinoma and liver metastases with gadoxetic acid enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. Radiology. 2011;260(2):446–53.

Chapter 28
EUS Evaluation of Pancreatic Cystic Lesions

Angeliki Machaira, Eleni Orfanoudaki, and Evangelos Kalaitzakis

Take Home Messages

- Pancreatic cystic lesions are diagnosed with increasing frequency as a result of an increase in the use of CT and MRI scans, with a reported prevalence of 2.4–21.5%
- EUS has a main role in pancreatic cystic lesion evaluation and its combination with EUS-guided FNA achieves higher diagnostic accuracy than MRI.
- Surveillance of pancreatic cystic lesions are mainly based on MRI and EUS is used as supplement in cases of lesions with worrisome features.

Pearls and Pitfalls

- Contrast-enhanced harmonic EUS, enables visualization of tissue microcirculation which may help discriminate viable neoplastic tissue from mucus, thus aiding the characterization of mural nodules in pancreatic cystic lesions.
- EUS alone has the same diagnostic accuracy with MRI.
- Cyst fluid cytology has very low sensitivity to identify malignancy (54%).
- EUS and EUS-FNA are low-risk, albeit invasive, procedures and may not be performed in all patients with a pancreatic cystic lesion.

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Future Perspectives

- The identification of molecular biomarkers that can be detected in pancreatic cystic fluid obtained by means of EUS-guided FNA may help determine pancreatic cyst type.
- EUS-guided microbiopsy through a standard FNA needle may help obtain a tissue diagnosis thus improving management of certain patient groups with pancreatic cystic lesions.
- Refinement of EUS-guided pancreatic cyst ablation techniques may improve the management of these patients, obviating the need for surgery.

28.1 Background

Pancreatic cystic lesions (PCLs) are usually asymptomatic and their detection is considered a result of the increased use of computed tomography (CT) and magnetic resonance imaging (MRI) for non-pancreatic indications, but also of the on-going improvement of the quality of cross-sectional imaging [1, 2]. The prevalence of pancreatic cysts varies from 2.4% [3] to 21.5% [4, 5] depending on the population studied and the imaging modalities used. Up to 47% of asymptomatic pancreatic cysts may be premalignant (or malignant) at the time of diagnosis [6] and the potential to detect pancreatic cancer in early, ideally precancerous, stages is the key to curative therapy or complete remission. The risk of malignant transformation of an incidental pancreatic cyst in the general population during 5 years is 0.7–2.5% per year [7], while the risk of operative mortality may, for some patients, be equivalent to that of malignancy [8]. Thus, the selection of patients who are to undergo more invasive diagnostic procedures and proceed to surgery is challenging.

The accuracy of CT and MRI scans to determine PCL type varies from 20% to 83% in different studies [9]. CT has a sensitivity and specificity of 36.3–71.4% and 64–100% in determining benign disease but an accuracy of making a specific diagnosis of 39–44.7%. MRI had a sensitivity of 91–100% and a specificity of 89.7% in assessing main pancreatic duct communication, an important feature that may determine the type of PCL [10, 11].

Endoscopic ultrasound (EUS) generates real-time high resolution images of PCLs providing morphological details that may aid in the identification of "suspicious" lesions. The diagnostic accuracy of EUS imaging alone for detecting malignant or premalignant lesions is reportedly 45–96% [12]. The combination of EUS with fine-needle aspiration (FNA) and the analysis of intracystic fluid as well as other ancillary techniques may further increase its diagnostic accuracy.

The aim of this chapter is to review the role of EUS in the diagnostic work-up, surveillance, and therapy of PCLs.

28.2 Classification of PCLs

PCLs may be classified as mucin-producing (intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystic neoplasms (MCNs)) which are considered premalignant lesions, or non-mucin-producing (simple cysts, pseudocysts, and serous cystic neoplasms (SCNs)), typically without malignant potential [11, 13]. Despite that other types of PCLs, that may be of concern for malignancy, exist, such as cystic neuroendocrine tumors and cystic pseudopapillary tumors, this categorization of PCLs is essential for subsequent work-up and decision-making for surveillance or surgical therapy. Table 28.1 summarizes the main characteristics of each PCL type.

Table 28.1 Major features of the most common cystic lesions

	Non-mucin producing		Mucin-producing	
Features	Pseudocyst	SCN	MCN	IPMN
Age at diagnosis	Variable	Middle aged	Middle aged	Elderly
Sex	M > F	F > M	F	M > F
Location	Any	Any	Body-tail	Head
Imaging characteristics	Unilocular Debris Communication with pancreatic duct Thick wall	Multilocular Lobulated Honeycomb	Multilocular Orange-like Septa Intramural nodules or solid component Thick wall	Multilocular (bunch of grapes) [14] Communication with pancreatic duct Septa Intramural nodules or solid component
Cyst fluid analysis	Low CEA (<192 ng/mL) High amylase	Low CEA (<192 ng/mL) Low amylase	High CEA (≥192 ng/mL) High amylase String sign[a]	High CEA (≥192 ng/mL) High amylase String sign[a]
Molecular markers	–	–	KRAS, p53, SMAD4	KRAS, GNAS, p53, PIK3CA, miRNAs
Malignant potential	None	Very rare	Moderate to high	Low to high

KRAS/GNAS/p53/SMAD4,PIK3CA,miRNAs: mutations that are linked to mucinous pancreatic cysts

CEA carcinoembryonic antigen, *MCN* mucinous cystic neoplasm, *IPMN* intraductal papillary mucinous neoplasm, *SCN* serous cystic neoplasm

[a]String sign: indirect test for cystic fluid viscosity assessment, performed by placing a sample of aspirated fluid between the thumb and index finger and measuring the length of stretch prior to disruption

28.3 Diagnostic Evaluation

28.3.1 EUS Imaging Characteristics of PCLs

Although cyst morphology on EUS is rarely typical for a certain cyst type [15] (Fig. 28.1), certain cyst features may provide clues as to cyst type and risk for malignancy. Cyst characteristics most commonly evaluated are size, presence of mural nodules, septations or solid masses, wall thickness, as well as the diameter of main pancreatic duct (MDP) and the presence of distal pancreatic atrophy [16, 17].

Generally, EUS imaging alone is accurate for diagnosing a benign from a malignant cyst in 65–96% of cases [18], which is similar to CT and MRI. However, EUS is superior in the identification specifically of mural nodules, which may indicate malignant transformation (14–75% positive predictive value for malignancy which increases in mural nodules >5 mm) [19–21]. Three EUS features discriminate mural nodules consisting of viable tissue compared to mucus: the latter is usually hypoechoic compared with adjacent soft tissue, smooth-edged, and has a hyperechoic rim. Body position change may be useful in distinguishing viable tissue from mucus during EUS [19] as the latter may be mobile. The same is also true for color doppler that may indicate blood flow in a mural nodule consisting of viable tissue [22].

Contrast-enhanced harmonic EUS may allow examination of the microcirculation and parenchymal perfusion without Doppler-related artifacts [22]. An intravenous microbubble contrast medium (galactose-palmitic acid, perfluorobutane, or sulfur hexafluoride) is used and the signal received by the transducer represents the nonlinear response of the microbubbles. It may help visualize blood flow in small blood vessels and recognize neoplastic neovasculature or thrombus-related vasculature obliteration [23]. Contrast-enhanced harmonic EUS is used mainly for investigation of solid pancreatic lesions, but it may also help identifying areas of malignant growth inside PCLs, allowing the possibility to distinguish mural nodules due to viable tumor tissue from mucus clots in mucinous PCLs or internal debris in

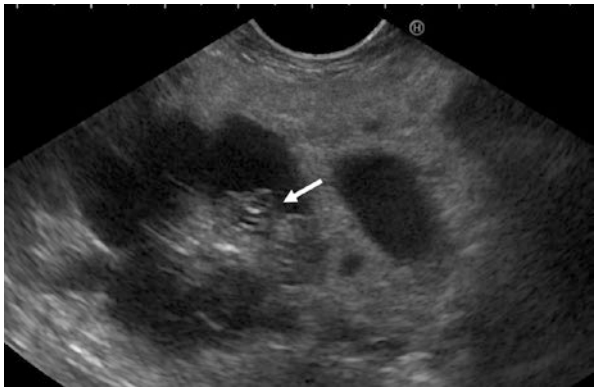

Fig. 28.1 Typical appearance of a serous cystadenoma in a female patient on EUS. A cystic lesion was noted in the body of the pancreas with central fibrous tissue (arrow)

pseudocysts [24, 25]. The addition of contrast-enhanced harmonic EUS to conventional Doppler EUS increases the specificity of the test from 40% up to 75% for recognition of mural nodules [26].

Other EUS morphologic findings including cyst size ≥3 cm, and pancreatic duct (PD) dilation can help identify patients likely to have malignant or borderline mucinous pancreatic cysts [27]. The estimated potential for malignancy in case of cyst size above 3 cm is 27–35% [1, 20, 21, 27]. However, the accuracy of EUS in size assessment may be inferior to other diagnostic modalities, particularly in the case of larger cysts that may not be visible in a single ultrasound plane and thus their size may be underestimated [28]. Other EUS features related to malignancy include the presence of a solid mass (56–89% positive predictive factor [1, 21]) (Fig. 28.2) and thickened cyst wall or thickened septations (33–75% positive predictive factor [1, 21, 27]). Dilation of the MPD (>5 mm) may raise the suspicion of a main duct-IPMN or mixed type IPMN [16] while the risk of malignancy reaches 51% [20, 27]. Identification of communication between the pancreatic duct and the PCL is suggestive of a pseudocyst or IPMN [29]. Unsurprisingly, the co-existence of distal pancreatic atrophy or lymphadenopathy with a PCL is a worrisome feature for malignancy [16].

28.3.2 EUS-Guided FNA

EUS-guided FNA is a safe procedure with reported complication rates of less than 2%. The ultrasound transducer on the distal tip of the linear array echoendoscope permits needle advancement into the PCL under real-time guidance (Fig. 28.3). Color doppler may be used to examine the projected path of the needle to avoid puncturing intervening blood vessels (Fig. 28.4). Complete cyst aspiration using only one needle pass is recommended whenever possible to reduce the risk of infection in the residual fluid [30]. The risk of infection from EUS-FNA of pancreatic cysts has been reported to be as 0.5–2% [31, 32]. Therefore, routine administration of i.v. antibiotics (fluoroquinolones or beta-lactam) is the standard of care, best given prior to or immediately after EUS-FNA followed by oral antibiotics for 3–5 days [30].

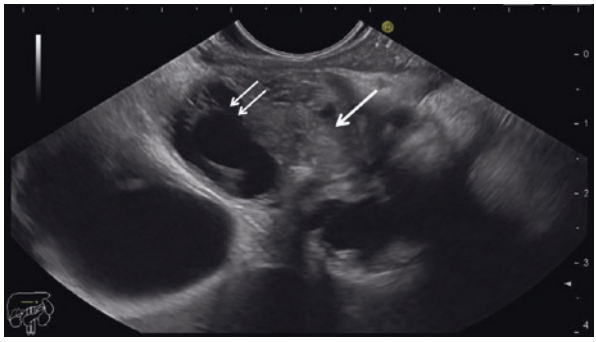

Fig. 28.2 Presence of solid mass (arrow) in a PCL (remaining cystic component indicated by double arrow). EUS-FNA was performed and the diagnosis of a malignant PCL was made (adenocarcinoma)

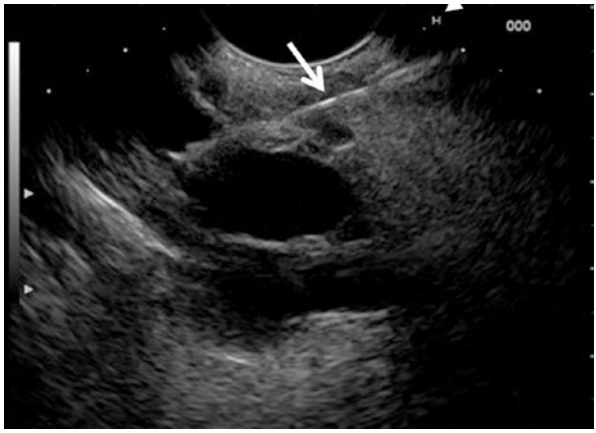

Fig. 28.3 EUS-guided FNA. A 22 gauge needle (arrow) is advanced into a pancreatic cystic lesion through the gastric wall under real-time ultrasound guidance in order to obtain a cystic fluid sample

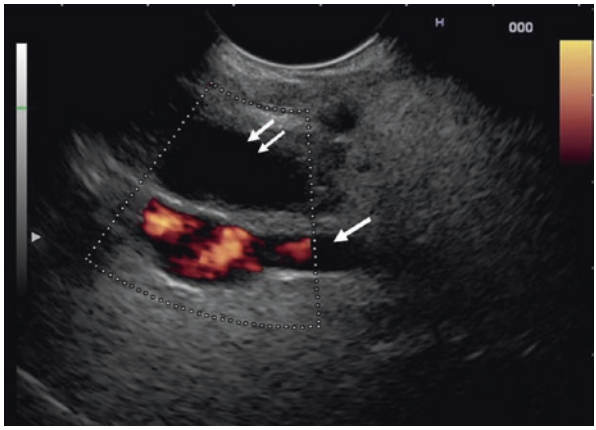

Fig. 28.4 Color Doppler ultrasound may be used to identify flow in blood vessels (arrow) while cystic lesions appear as anechoic areas (double arrow)

28.3.3 Cystic Fluid Analysis

Cyst fluid analysis is useful in the differential diagnosis between mucinous and non-mucinous PCLs with specificity (95–98%), but moderate sensitivity (44–50%) and accuracy (65–79%) [33]. Fluid evaluation is based on its viscosity, the presence of extracellular mucin, the level of tumor markers (CEA, CA19-9, etc.) and enzymes (amylase), cytology, and, in specialist centers, molecular analysis.

Viscosity is usually lower in pseudocysts and serous cystadenomas compared with mucinous lesions such as MCN, IPMN, or mucinous cystadenocarcinoma. The "string sign" is a simple indirect test for viscosity assessment. The test is performed by placing a drop of aspirated cyst fluid between the thumb and index finger and measuring the length of stretch prior to disruption [34]. Non-mucinous lesions have

a median string length of 0 mm compared with a median length of 3.5 mm in mucinous lesions [13, 34]. The sensitivity and specificity of the string sign for diagnosis of mucinous cysts is 58% and 95% [35].

Among the tumor markers, cyst fluid analysis for CEA is commonly performed [36]. The usual cut-off is 192 ng/dl with a reported sensitivity of 52–78% and specificity of 63–91% for diagnosing mucinous PCLs [37–39]. Amylase may be measured in cystic fluid and it may indicate communication with the pancreatic duct. Thus, high cystic fluid amylase levels commonly suggest the existence of a pseudocyst or an IPMN. However, in practice, amylase levels may vary widely in different PCLs and, therefore, its main utility in clinical practice is limited to the exclusion of a pseudocyst in the event of low levels (<250 U/L sensitivity 44%, specificity 98%) [33, 40].

Cyst fluid cytology may identify the presence of high-grade dysplasia or pancreatic cancer [41]. However, cyst fluid is frequently acellular and the sensitivity of cytology for diagnosing malignant PCLs is only 54% with a specificity of 93% [42, 43]. The sole detection of atypical epithelial cells in cystic fluid is considered a "worrisome feature" according to recent guidelines for the management of PCLs [16, 44, 45].

28.3.4 Molecular Biomarkers in Pancreatic Cystic Fluid

The potential clinical utility of molecular marker analysis in PCL fluid is propitious, but still under investigation. As the pathophysiology of PCLs evolves, new molecular biomarkers are identified that, along with cyst fluid analyses for viscosity, amylase and CEA, may aid in the characterization of PCLs [46]. The improvement of DNA analysis methods with techniques such as next generation sequencing (NGS), has been crucial as they may improve accuracy by allowing processing multiple DNA sequences from very small specimens [47, 48].

Mutations mostly studied in PCLs are located in the KRAS and GNAS genes. Activating point mutations in KRAS, an oncogene coding for a GTP-binding protein important in several intracellular pathways, may be a molecular biomarker identifying mucinous cysts (both MCN and IPMN) with a specificity of 80–96% and sensitivity of 50–54% [49, 50]. Activating mutations in GNAS, an oncogene encoding for a stimulatory G-protein enhancing cell proliferation and growth, is a highly specific test for IPMN [51]. Thus, the combination of GNAS and KRAS testing is highly specific (100%) and moderately sensitive (65%) for IPMNs [36]. Other promising molecular markers under investigation include mutations in p53, a tumor suppressor gene located in chromosome 17p, found in MCN and IPMNs with high grade dysplasia or invasive carcinoma. Mutations in CDKN2A and in PIK3CA, also tumor suppressor genes located in chromosome 9p21 and 3q26.3, are found mostly in IPMNs, and mutations in SMAD4 located in chromosome 18q21.1 are specific for MCNs. Finally, miRNA analyses (small, noncoding RNA molecules involved in

regulating gene expression at the post-transcriptional level, such as miRNA-21, miRNA-155, miRNA-221, miRNA-17-3p) have also been reported to be useful in the differential diagnosis of IPMNs and their progression to malignancy, but also able to predict cyst pathology with sensitivity 89% and specificity 100% [46].

Mutation analysis along with conventional tests, such as CEA amylase, and cytology, may improve the diagnostic accuracy of cyst fluid analyses [51, 52] (Table 28.1). Integrated molecular pathology (IMP) testing, that involves combination of molecular analyses with first-line test results (cytology, imaging, and fluid chemistry), has proved to be highly reliable in the differentiation between PCLs with vs. those without potential for malignant transformation, being superior to cytology or the 2012 Sendai criteria alone [53]. After IMP testing, PCLs are classified in four groups (benign, statistically indolent, statistically at higher risk, and aggressive) according to the number of molecular criteria *(a single high-clonality mutation, elevated level of high-quality DNA, multiple low-clonality mutations; a single low-clonality oncogene mutation)* and clinical features *(cyst size >3 cm, growth rate >3 mm/year, duct dilation >1 cm, carcinoembryonic antigen level >1000 ng/mL, cytologic evidence of high-grade dysplasia)* they may meet [53]. The results of the initial report are promising showing improvement in accuracy (89.6%), sensitivity (83.3%), and specificity (90.6%) compared to the 2012 Sendai criteria accuracy (52.2%), sensitivity (90.9%), and specificity (46.2%). The influence of IMP on real-world management decisions may lead to amelioration of surveillance and higher confidence in surgery decisions [54].

Although very promising, molecular analyses have not been integrated in international guidelines and are currently available only in expert centers.

28.3.5 EUS-Guided Microbiopsy of the Pancreatic Cystic Wall

EUS-guided microbiopsy is a new promising procedure which is based on analysis of cystic wall tissue (or that of a mural nodule) obtained by means of a novel microbiopsy forceps inserted through a conventional 19 G FNA needle [55]. The clinical success rate using EUS-guided microbiopsy has been reported to be much higher than standard EUS-FNA, 77–80.4% vs. 25–31%, respectively [56, 57]. Furthermore, microbiopsy offers good quality sample achieving more accurate diagnosis of PCL type compared with FNA with (clinical success of 71.4%) [55, 58]. Also, NGS of microbiopsy specimens for the detection of molecular biomarkers is a promising method that has the potential to improve diagnostic decision making [59, 60]. On the other hand, the procedure has been reported to be associated with a 9.9% adverse event rate, most frequently acute pancreatitis, with 2% being severe [57]. Although EUS-guided microbiopsy seems to be a promising tool in the diagnostic work-up of PCLs, it is not established in clinical practice and, in view of the related complication rate, it may not be considered part of the standard investigation of all patients with PCLs. Further studies are needed to define subgroups of patients that would benefit from the procedure despite the risk for complications [61, 62].

28.3.6 Needle-Based Confocal Laser Endomicroscopy (nCLE)

Needle-based confocal laser endomicroscopy (nCLE) enables real-time imaging of the inner wall of PCL during EUS. It is a novel imaging technique which allows to obtain in vivo histopathology images with a CLE miniprobe via 19-G EUS-FNA needle. Intravenous fluorescein is used during nCLE to enhance blood vessels and other structures within the pancreatic cysts. The performance of nCLE for the differential diagnosis of mucinous vs. non-mucinous PCLs is greater than cyst fluid analysis (CEA, amylase, KRAS, GNAS, and cytology) achieving a sensitivity of 98%, a specificity of 94%, and an accuracy of 97% [63, 64]. The incidence of adverse events is 5% [58, 64]. Limitations of the technique include high cost and the need for endoscopists trained in histopathology, but the opportunity of a direct accurate diagnosis is appealing. Further studies on the utility of the technique and its cost-effectiveness are needed, but it is promising as a potential complement to EUS and analysis of cystic fluid obtained by FNA [65].

28.4 Work-Up of PCLs and Current Guidelines

Challenges in the differential diagnosis of PCLs have led several national and international associations to issue guidelines for the management of these lesions and the role of EUS in their work-up (Table 28.2). All guidelines recognize that EUS, as an invasive procedure, may not possibly be performed in all patients with a PCL. Other types of cross-sectional imaging, most commonly MRI, are more appropriate as first-line investigations. EUS with FNA and subsequent fluid analysis is reserved for a selected subset of patients meeting specific criteria often designated as "worrisome features" (Table 28.2).

28.5 Surveillance of PCLs

PCL surveillance is mainly based on MRI, as a non-invasive imaging modality with a favorable safety profile due to lack of radiation exposure. However, EUS may be an alternative test when MRI is contraindicated or when progression is suspected (e.g. cyst growth or development of other worrisome features during follow-up).

Cyst surveillance should be offered to surgically fit candidates with asymptomatic cysts and ideally it should be tailored to patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference. The suggested follow-up plan varies according to cyst type and size, and the presence of worrisome features [67]. Follow-up recommendations vary among different published guidelines (Table 28.3).

Table 28.2 Clinical guidelines comparison of four different associations *[Fukuoka guidelines, European guidelines, American Gastroenterology Association (AGA) guidelines, American College of Gastroenterology guidelines (ACG)]*

	Fukuoka guidelines (2017) [16]	European guidelines (2018) [21]	AGA guidelines (2015) [66]	ACG (2018) [11]
Indications for immediate surgical removal	**"High risk stigmata"** • Obstructive jaundice in a patient with cystic lesion of the head of the pancreas • Enhancing mural nodule >5 mm • Main pancreatic duct >10 mm Cytology: suspicious or positive for malignancy	• Tumor related obstructive jaundice • Enhancing mural nodules (≥5 mm) • Solid mass • MPD dilation ≥10 mm Positive cytology for malignancy or HGD	• Solid component associated with the cyst **AND** • Dilated MPD (no size criteria) **AND/OR** • Concerning features of EUS (positive cytology)	Findings after EUS/FNA: • Mural nodule • Main duct involvement/ patulous ampulla • Cytology with high-grade dysplasia or pancreatic cancer
Indications for EUS-FNA and close surveillance/ relative indication for surgery	**"Worrisome features"** • Cyst >3 cm • Enhancing mural nodule <5 mm • Thickened/enhancing cyst walls • Main duct size 5–9 mm • Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy • Pancreatitis • Lymphadenopathy • Increased serum level of CA19-9 • Cyst growth rate >5 mm/2 years	• Cyst diameter ≥40 mm • Enhancing mural nodules (<5 mm) • MPD dilation between 5 and 9.9 mm • Acute pancreatitis (caused by IPMN) • New onset of diabetes mellitus • Increased level of serum CA 19-9 (>37 U/mL) • Cystic growth rate ≥5 mm/ year	• Cyst >3 cm • Solid component associated with the cyst • Dilated MPD (no size criteria)	• Obstructive jaundice • Cyst ≥3 cm • Associated solid mass/ mural nodule • Main duct diameter >5 mm • Change in main duct caliber with upstream atrophy • Acute pancreatitis secondary to pancreatic cyst • Increased serum level Ca 19-9

HGD high grade dysplasia, *MPD* main pancreatic duct

In general, PCLs of uncertain type without worrisome features must be followed up with MRI or EUS every 6 months to 2 years depending on their size and clinical characteristics (Table 28.3). PCLs with worrisome features but without a clear diagnosis of malignancy are commonly considered for close surveillance with alternating MRI and EUS every 3–6 months. After pancreatic resection for an IPMN, lifelong surveillance with MRI or EUS is recommended (Table 28.3).

Table 28.3 Surveillance guidelines of four different associations *[Fukuoka guidelines, European guidelines, American Gastroenterology Association (AGA) guidelines, American College of Gastroenterology guidelines (ACG)]*

	Fukuoka guidelines 2017 [16]	European guidelines 2018 [21]	AGA guidelines 2015 [66]	ACG (2018) [11]
Cyst size	**<1 cm**: CT/MRI in 6 months, then every 2 years if no change **1–2 cm**: CT/MRI every 6 months for 1 year, every year for 2 years, then lengthen interval up to 2 years if no change **2–3 cm**: EUS in 3–6 months, then lengthen interval up to 1 year, alternating MRI with EUS as appropriate **>3 cm**: Close surveillance alternating MRI with EUS every 3–6 months.	**<15 mm**: MRI/EUS every year → after 3 years with stable findings → every 2 years **>15 mm**: MRI/EUS every 6 months → after 1 year stable findings → every year	Absence of concerning EUS-FNA results → MRI after 1 year and then every 2 years If significant changes are detected → EUS-FNA	**<1 cm**: MRI every 2 years × 4 years and then lengthening interval imaging **1–2 cm**: MRI every 1 year × 3, and then every 2 years for 4 years and then lengthening interval imaging **2–3 cm**: MRI or EUS in 6–12 months × 3 years, and then MRI every 1 year × 4 and then lengthening interval imaging **>3 cm**: MRI alternating with EUS every 6 months × 3 years, and then MRI alternating with EUS every 1 year × 4 years, and then lengthening interval imaging
Duration of surveillance	Life-long	Life-long	May discontinue after 5 years with stable findings	Life-long
Surveillance after surgery	IPMN → MRI/EUS every 6 months MCN → no surveillance Benign cysts → no surveillance	IPMN → MRI/EUS	Finding of invasive cancer or high dysplasia in cyst → MRI/EUS every 2 years Absence of malignancy or high grade dysplasia → no surveillance	IPMN → MRI every 2 years MCN → no surveillance SCN, pseudocyst, benign cyst → no surveillance

MCN mucinous cystic neoplasm, *IPMN* intraductal papillary mucinous neoplasm, *SCN* serous cystic neoplasm

28.6 EUS-Guided Cyst Ablation Therapy

Patients with a neoplastic PCL with an indication for surgery but who are poor surgical candidates (or those who refuse surgery) may potentially benefit from EUS-guided cyst ablation [68]. This is usually performed by replacing the fluid content of cystic tumors with ethanol, often in combination with intracystic infusion of chemotherapeutic agents [69]. Complete remission has been reported after 6 years of follow-up in 60–79% following EUS-guided ablation therapy with ethanol and paclitaxel [70, 71]. Adverse events are not uncommon (~12–26%) and include fever, abdominal pain, acute pancreatitis, peritonitis, and splenic and/or portal vein thrombosis [71]. Recently, ablation with paclitaxel or gemcitabine alone has been reported with similar efficacy but fewer adverse effects (reduction from 21% to 15%) [72, 73]. Most studies have included patients with PCLs without septations or communication with the pancreatic duct and above a certain size allowing to effectively empty the cyst and replace the volume removed with ethanol and/or chemotherapeutic agents (Table 28.4) [74]. Prophylactic antibiotics (fluoroquinolones or beta-lactamase) for 3–5 days are recommended to prevent post-procedural infection [75].

Another method for EUS-guided cyst ablation is endoscopic radiofrequency ablation [76], employing hyper-thermal energy resulting in disruption of the tumour microenvironment and cell membranes with subsequent necrosis of the neoplastic epithelium [69]. Response rate has been reported to be 71%, but only 65% have complete remission after a mean/median follow-up of 12 months. Adverse events occur in 10% including mainly acute pancreatitis and infection but also other rare events such as jejunal perforation [76].

However, studies published thus far included a limited number of patients and, however promising, the role of EUS-guided cyst ablation therapy is still under investigation [75].

Table 28.4 Characteristics of pancreatic cystic lesion suitable for ablation therapy

Indications	Contraindications
Unilocular/Oligolocular mucinous pancreatic cyst	Enhancing mural nodules, solid components within the cysts, thick walls, thick septations
Size >2–3 cm	Dilated main pancreatic >5 mm or communication of the cyst with the main pancreatic duct
	MPD stricture with pancreatic tail atrophy, pancreatic necrosis, medical history of acute pancreatitis

MDP main pancreatic duct

28.7 Summary

The main goal in management of PCLs is accurate identification of patients with cancer or at risk for malignancy so that unnecessary surgery is minimized, adequate follow-up is planned, and, in appropriate cases, curative surgery is performed without delay. EUS has an important role in the differential diagnosis and surveillance of PCLs, while its potential role in the endoscopic treatment of these patients is evolving.

Conflicts of Interest None

References

1. Robles EP-C, Maire F, Cros J, Vullierme M-P, Rebours V, Sauvanet A, et al. Accuracy of 2012 International Consensus Guidelines for the prediction of malignancy of branch-duct intraductal papillary mucinous neoplasms of the pancreas. United European Gastroenterol J. 2016;4(4):580–6.
2. Moris M, Bridges MD, Pooley RA, Raimondo M, Woodward TA, Stauffer JA, et al. Association between advances in high-resolution cross-section imaging technologies and increase in prevalence of pancreatic cysts from 2005 to 2014. Clin Gastroenterol Hepatol. 2016;14(4):585–93.e3.
3. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CHJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8(9):806–11.
4. Sey MS, Teagarden S, Settles D, McGreevy K, Cote GA, Sherman S, et al. Prospective cross-sectional study of the prevalence of incidental pancreatic cysts during routine outpatient endoscopic ultrasound. Pancreas. 2015;44(7):1130–3.
5. Martínez B, Martínez JF, Aparicio JR. Prevalence of incidental pancreatic cyst on upper endoscopic ultrasound. Ann Gastroenterol. 2018;31(1):90–5.
6. Lee K, Sekhar A, Rofsky N, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105:2079–84.
7. Kromrey M-L, Bülow R, Hübner J, Paperlein C, Lerch MM, Ittermann T, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. Gut. 2018;67(1):138–45.
8. Gaujoux S, Brennan MF, Gonen M, D'Angelica MI, DeMatteo R, Fong Y, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am Coll Surg. 2011;212(4):590–600; discussion 3.
9. Berland LL, Silverman SG, Gore RM, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol. 2010;7(10):754–73. https://doi.org/10.1016/j.jacr.2010.06.013.
10. Jones M, Buchanan AS, Neal C, Dennison A, Metcalfe MS, Garcea G. Imaging of indeterminate pancreatic cystic lesions: a systematic review. Pancreatology. 2013;13:436–42.

11. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113(4):464–79.
12. Muthusamy VR, Chandrasekhara V, Acosta RD, Bruining DH, Chathadi KV, Eloubeidi MA, et al. The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms. Gastrointest Endosc. 2016;84(1):1–9.
13. WGO Review Team, Malagelada J, Guda N, Goh K-L, Hackert T, Layer P, Molero X, Pandol S, Tanaka M, Umar M, LeMair A. Pancreatic cystic lesions - World Gastroenterology Organisation global guidelines. Milwaukee, WI: World Gastroenterology Organisation; 2019.
14. Kovač J, Janković A, Mašulović D. The "bunch of grapes" pattern of branch-duct IPMN. Abdom Radiol. 2020;45:249.
15. Barresi L, Tarantino I, Granata A, Curcio G, Traina M. Pancreatic cystic lesions: how endoscopic ultrasound morphology and endoscopic ultrasound fine needle aspiration help unlock the diagnostic puzzle. World J Gastrointest Endosc. 2012;4(6):247–59.
16. Tanaka M, Fernández-del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17(5):738–53.
17. Ridtitid W, DeWitt JM, Schmidt CM, Roch A, Stuart JS, Sherman S, et al. Management of branch-duct intraductal papillary mucinous neoplasms: a large single-center study to assess predictors of malignancy and long-term outcomes. Gastrointest Endosc. 2016;84(3):436–45.
18. Tirkes T, Aisen AM, Cramer HM, Zyromski NJ, Sandrasegaran K, Akisik F. Cystic neoplasms of the pancreas; findings on magnetic resonance imaging with pathological, surgical, and clinical correlation. Abdom Imaging. 2014;39(5):1088–101.
19. Zhong N, Zhang L, Takahashi N, Shalmiyev V, Canto MI, Clain JE, et al. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. Clin Gastroenterol Hepatol. 2012;10(2):192–8.e2.
20. Kim TH, Song TJ, Hwang J-h, Yoo K-s, Lee W-j, Lee K-h, et al. Predictors of malignancy in pure branch duct type intraductal papillary mucinous neoplasm of the pancreas: a nationwide multicenter study. Pancreatology. 2015;15(4):405–10.
21. The European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67(5):789–804.
22. Kitano M, Sakamoto H, Komaki T, Kudo M. New techniques and future perspective of EUS for the differential diagnosis of pancreatic malignancies: contrast harmonic imaging. Dig Endosc. 2011;23(s1):46–50.
23. Zhong L, Chai N, Linghu E, Li H, Yang J, Tang P. A prospective study on contrast-enhanced endoscopic ultrasound for differential diagnosis of pancreatic cystic neoplasms. Dig Dis Sci. 2019;64(12):3616–22.
24. Hocke M, Cui X-W, Domagk D, Ignee A, Dietrich CF. Pancreatic cystic lesions: the value of contrast-enhanced endoscopic ultrasound to influence the clinical pathway. Endosc Ultrasound. 2014;3(2):123–30.
25. Fujita M, Itoi T, Ikeuchi N, Sofuni A, Tsuchiya T, Ishii K, et al. Effectiveness of contrast-enhanced endoscopic ultrasound for detecting mural nodules in intraductal papillary mucinous neoplasm of the pancreas and for making therapeutic decisions. Endosc Ultrasound. 2016;5(6):377–83.
26. Kamata K, Kitano M, Omoto S, Kadosaka K, Miyata T, Yamao K, et al. Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of pancreatic cysts. Endoscopy. 2016;48(01):35–41.
27. Javia S, Munigala S, Guha S, Agarwal B. EUS morphology is reliable in selecting patients with mucinous pancreatic cyst(s) most likely to benefit from surgical resection. Gastroenterol Res Pract. 2017;2017:8.
28. Lee YS, Paik K-H, Kim HW, Lee J-C, Kim J, Hwang J-H. Comparison of endoscopic ultrasonography, computed tomography, and magnetic resonance imaging for pancreas cystic lesions. Medicine (Baltimore). 2015;94(41):e1666.

29. Hijioka S, Hara K, Mizuno N, Imaoka H, Bhatia V, Yamao K. Morphological differentiation and follow-up of pancreatic cystic neoplasms using endoscopic ultrasound. Endosc Ultrasound. 2015;4(4):312–8.
30. Polkowski M, Jenssen C, Kaye P, Carrara S, Deprez P, Gines A, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Guideline - March 2017. Endoscopy. 2017;49(10):989–1006.
31. Hashimoto R, Lee JG. Concise commentary: antibiotic prophylaxis for endoscopic needle aspiration of pancreatic cystic lesions: bursting the bubble? Dig Dis Sci. 2019;64(8):2316–7.
32. Jenssen C, Alvarez-Sánchez MV, Napoléon B, Faiss S. Diagnostic endoscopic ultrasonography: assessment of safety and prevention of complications. World J Gastroenterol. 2012;18(34):4659–76.
33. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62(3):383–9.
34. Leung KK, Ross WA, Evans D, et al. Pancreatic cystic neoplasm: the role of cyst morphology, cyst fluid analysis, and expectant management. Ann Surg Oncol. 2009;16(10):2818–24.
35. Bick BL, Enders FT, Levy MJ, Zhang L, Henry MR, Abu Dayyeh BK, et al. The string sign for diagnosis of mucinous pancreatic cysts. Endoscopy. 2015;47(7):626–31.
36. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330–6.
37. Park WG, Mascarenhas R, Palaez-Luna M, et al. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. Pancreas. 2011;40(1):42–5.
38. Al-Haddad M, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, et al. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. Gastrointest Endosc. 2014;79(1):79–87.
39. Cizginer S, Turner BG, Bilge AR, Karaca C, Pitman MB, Brugge WR. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas. 2011;40(7):1024–8.
40. Al-Rashdan A, Schmidt CM, Al-Haddad M, McHenry L, Leblanc JK, Sherman S, et al. Fluid analysis prior to surgical resection of suspected mucinous pancreatic cysts. A single centre experience. J Gastrointest Oncol. 2011;2(4):208–14.
41. Genevay M, Mino-Kenudson M, Yaeger K, Konstantinidis IT, Ferrone CR, Thayer S, et al. Cytology adds value to imaging studies for risk assessment of malignancy in pancreatic mucinous cysts. Ann Surg. 2011;254(6):977–83.
42. Thornton GD, McPhail MJW, Nayagam S, Hewitt MJ, Vlavianos P, Monahan KJ. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. Pancreatology. 2013;13(1):48–57.
43. Thosani N, Thosani S, Qiao W, Fleming JB, Bhutani MS, Guha S. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. Dig Dis Sci. 2010;55(10):2756–66.
44. Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, Mino-Kenudson M, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol. 2010;118(6):434–40.
45. Hoda RS, Lu R, Arpin RN, Rosenbaum MW, Pitman MB. Risk of malignancy in pancreatic cysts with cytology of high-grade epithelial atypia. Cancer Cytopathol. 2018;126(9):773–81.
46. Plougmann JI, Klausen P, Karstensen JG, Vilmann P, Hasselby JP, Hansen CP, et al. Molecular biomarkers have the potential to improve the diagnostic work-up of pancreatic cystic lesions. Scand J Gastroenterol. 2017;52(9):932–40.
47. Jones M, Zheng Z, Wang J, Dudley J, Albanese E, Kadayifci A, et al. Impact of next-generation sequencing on the clinical diagnosis of pancreatic cysts. Gastrointest Endosc. 2016;83(1):140–8.

48. Amato E, Molin MD, Mafficini A, Yu J, Malleo G, Rusev B, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol. 2014;233(3):217–27.
49. Singhi AD, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, et al. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. Gut. 2018;67(12):2131–41.
50. Al-Haddad M. Role of emerging molecular markers in pancreatic cyst fluid. Endosc Ultrasound. 2015;4(4):276–83.
51. Rosenbaum MW, Jones M, Dudley JC, Le LP, Iafrate AJ, Pitman MB. Next-generation sequencing adds value to the preoperative diagnosis of pancreatic cysts. Cancer Cytopathol. 2017;125(1):41–7.
52. Gillis A, Cipollone I, Cousins G, Conlon K. Does EUS-FNA molecular analysis carry additional value when compared to cytology in the diagnosis of pancreatic cystic neoplasm? A systematic review. HPB (Oxford). 2015;17(5):377–86.
53. Al-Haddad MA, Kowalski T, Siddiqui A, Mertz HR, Mallat D, Haddad N, et al. Integrated molecular pathology accurately determines the malignant potential of pancreatic cysts. Endoscopy. 2015;47(02):136–46.
54. Loren D, Kowalski T, Siddiqui A, Jackson S, Toney N, Malhotra N, et al. Influence of integrated molecular pathology test results on real-world management decisions for patients with pancreatic cysts: analysis of data from a national registry cohort. Diagn Pathol. 2016;11:5.
55. Kovacevic B, Klausen P, Hasselby JP, Karstensen JG, Rift CV, Kalaitzakis E, et al. A novel endoscopic ultrasound-guided through-the-needle microbiopsy procedure improves diagnosis of pancreatic cystic lesions. Endoscopy. 2018;50(11):1105–11.
56. Hashimoto R, Lee JG, Chang KJ, Chehade NEH, Samarasena JB. Endoscopic ultrasound-through-the-needle biopsy in pancreatic cystic lesions: a large single center experience. World J Gastrointest Endosc. 2019;11(11):531–40.
57. Late breaking abstracts - LB10. Clinical impact of endoscopic ultrasound-guided through-the-needle microbiopsies in patients with pancreatic cysts – a prospective single-center study. United European Gastroenterol J. 2019;7(10):1411–25.
58. Kohoutova D, Zar S, Repak R, Vlavianos P, Bures J. Pancreatic cysts: diagnostic role of EUS-guided microforceps biopsy and confocal laser endomicroscopy. Gastroenterol Res Pract. 2019;2019:3431048.
59. Charlotte Vestrup Rift BK, Melchior LC. Late breaking abstracts-feasibility of next generation sequencing of endoscopic ultrasound guided microbiopsies from pancreatic cystic neoplasms. United European Gastroenterol J. 2019;7(8 Suppl)
60. Vestrup Rift C, Melchior LC, Kovacevic B, Toxværd A, Klausen P, Karstensen JG, et al. Next-generation sequencing of endoscopic ultrasound guided microbiopsies from pancreatic cystic neoplasms. Histopathology. 2019;75(5):767–71.
61. Kovacevic B, Karstensen JG, Havre RF, Pham KD-C, Giovannini M, Dabizzi E, et al. Initial experience with EUS-guided microbiopsy forceps in diagnosing pancreatic cystic lesions: a multicenter feasibility study (with video). Endosc Ultrasound. 2018;7(6):383–8.
62. Faias S, Pereira L, Luís Â, Chaves P, Cravo M. Genetic testing vs microforceps biopsy in pancreatic cysts: systematic review and meta-analysis. World J Gastroenterol. 2019;25:3450–67.
63. Napoleon B, Palazzo M, Lemaistre A-I, Caillol F, Palazzo L, Aubert A, et al. Needle-based confocal laser endomicroscopy of pancreatic cystic lesions: a prospective multicenter validation study in patients with definite diagnosis. Endoscopy. 2019;51(09):825–35.
64. Krishna SG, Hart PA, Malli A, Kruger AJ, McCarthy ST, El-Dika S, et al. Endoscopic ultrasound-guided confocal laser endomicroscopy increases accuracy of differentiation of pancreatic cystic lesions. Clin Gastroenterol Hepatol. 2020;18(2):432–40.e6.
65. Napoleon B, Pujol B, Palazzo M, Caillol F, Palazzo L, Aubert A, et al. Needle-based confocal laser endomicroscopy (nCLE) for the diagnosis of pancreatic cystic lesions: preliminary results of the first prospective multicenter study. Gastroenterology. 2017;152(5):S132–S3.

66. Vege SS, Ziring B, Jain R, Moayyedi P, Adams MA, Dorn SD, et al. American Gastroenterological Association Institute Guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):819–22.
67. Kim GE, Shin SS, Kim JW, Heo SH, Lim HS, Jun CH, et al. Incidental, small (<3 cm), unilocular, pancreatic cysts: factors that predict lesion progression during imaging surveillance. Korean J Radiol. 2017;18(6):915–25.
68. Park JK, Song BJ, Ryu JK, Paik WH, Park JM, Kim J, et al. Clinical outcomes of endoscopic ultrasonography–guided pancreatic cyst ablation. Pancreas. 2016;45(6):889–94.
69. Signoretti M, Valente R, Repici A, Delle Fave G, Capurso G, Carrara S. Endoscopy-guided ablation of pancreatic lesions: technical possibilities and clinical outlook. World J Gastrointest Endosc. 2017;9(2):41–54.
70. Choi JH, Seo DW, Song TJ, Park DH, Lee SS, Lee SK, et al. Long-term outcomes after endoscopic ultrasound-guided ablation of pancreatic cysts. Endoscopy. 2017;49(9):866–73.
71. DeWitt JM, Al-Haddad M, Sherman S, LeBlanc J, Schmidt CM, Sandrasegaran K, et al. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. Endoscopy. 2014;46(06):457–64.
72. Moyer MT, Sharzehi S, Mathew A, Levenick JM, Headlee BD, Blandford JT, et al. The safety and efficacy of an alcohol-free pancreatic cyst ablation protocol. Gastroenterology. 2017;153(5):1295–303.
73. Moyer MT, Dye CE, Sharzehi S, Ancrile B, Mathew A, McGarrity TJ, et al. Is alcohol required for effective pancreatic cyst ablation? The prospective randomized CHARM trial pilot study. Endosc Int Open. 2016;4(5):E603–E7.
74. Teoh AY-B, Seo DW, Brugge W, Dewitt J, Kongkam P, Linghu E, et al. Position statement on EUS-guided ablation of pancreatic cystic neoplasms from an international expert panel. Endosc Int Open. 2019;7(9):E1064–E77.
75. Attila T, Adsay V, Faigel DO. The efficacy and safety of endoscopic ultrasound-guided ablation of pancreatic cysts with alcohol and paclitaxel: a systematic review. Eur J Gastroenterol Hepatol. 2019;31(1):1–9.
76. Barthet M, Giovannini M, Lesavre N, Boustiere C, Napoleon B, Koch S, et al. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. Endoscopy. 2019;51(9):836–42.

Chapter 29
Imaging After Neoadjuvant Therapy

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Take Home Messages

- After neoadjuvant therapy, most patients show stable disease at imaging and about 20% have partial response. Progression of disease is reported in about 16%.
- Cross-sectional imaging overestimates the amount of residual viable tumour around vessels and thus cannot reliably predict resectability
- Functional imaging may depict tumour activity under therapy, but currently lacks the spatial resolution to detect microscopic disease at the crucial interface of mass and vessel wall

Pearls and Pitfalls

- After neoadjuvant therapy, a persistent tissue cuff around crucial vessels is not correlated to histopathologic margins
- There is no consensus on absolute sizes, size dynamics or grey level intensities predicting margin-free resection; most research focuses on tumours of less than 3 cm.
- Imaging correlates of tumour biology under therapy are increasingly investigated

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Future Perspectives

- Detection of subtle changes after therapy needs enhanced tissue differentiation on CT and better special resolution in functional imaging (diffusion-weighted MRI and PET-CT)
- Several methods of diffusion-weighted imaging are tested to increase specificity for residual tumour versus inflammation and oedema, the most widely investigated being intravoxel incoherent motion (IVIM) diffusion-weighted imaging (DWI)
- Quantifying tumour heterogeneity with texture analysis software tools is another thriving approach to translate tumour behaviour into imaging ('radiomics' science).

29.1 Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is categorized into three surgical stages at the time of diagnosis if no distant metastasis is present: resectable, borderline resectable, and locally advanced [1], and the benefit of neoadjuvant therapy on pancreatic adenocarcinoma is currently subject of intensive clinical research [2, 3]. Since the recognition of borderline resectable disease in 2008 [4], neoadjuvant concepts have been implemented in order to achieve downstaging from either borderline resectable or locally advanced/non-resectable PDAC to a more favourable surgical stage, while in a more recent development, neoadjuvant therapy in the setting of resectable PDAC has equally gained momentum [5–7]. Gemcitabine-based regimens combined with nab-paclitaxel [8], and the advent of FOLFIRINOX-based schemes in 2011 [9], both with or without additional chemoradiation, hold promise for downstaging PDAC and more importantly, enhance the rate of margin-free (R0) resection [10–12].

Unfortunately, response evaluation on imaging and prediction of resectability has proven challenging due to inhomogeneous tumour replacement, mainly by fibrosis [13]. Although CA 19-9 levels and clinical performance status are incorporated into reassessment [1], multiphase contrast-enhanced multidetector CT (MDCT) with three-dimensional reconstructions remains the mainstay for further patient selection for surgery [14]. Meanwhile, advances in magnetic resonance imaging (MRI), notably faster acquisition techniques and enhanced image quality have brought MRI close to the spatial resolution of MDCT, while offering superior contrast resolution and the opportunities of functional imaging in terms of diffusion-weighted imaging (DWI) [15].

29.2 Impact of Histopathologic Response Patterns on Imaging

It was early recognized that NAT-induced tumour cell injury in PDAC is mainly reflected by isovolumetric tissue replacement with fibrous stroma, inflammation and extracellular matrix, rather than volume loss [13, 16]. In 1992, Evans at al.

reported the histologic changes in 17 resected specimens after NAT and established a pathologic response grading system for PDAC [17] by describing the percentage of viable tumour cells within the specimen. However, Evan's proposal is derived from response assessment in other organ systems, causing some criticism over hypothesized analogies to adenocarcinomas of the pancreas [18]. In their review, Kalimuthu et al. outlined histopathologic changes after NAT with emphasis on subtle residual tumour nests scattered throughout fibrosis [19].

New insights into the biology of PDAC reveal complex interactions of stroma, extracellular matrix, inflammation, and tumour cells [20]. This histopathologic heterogeneity of response, and non-discernible microstructure invasion is thought to cause failures in predicting viable tumour around crucial surgical structures [21–24]. Meta-analyses of histopathology after NAT of note, found lower rates of perineural invasion [11, 25] and a rate of complete pathologic response of 2–7% [26, 27].

29.3 Imaging Response Assessment with RECIST1.1 (Clinical Stage)

Owing to the specific tumour spread of PDAC, metric re-assessment using RECIST1.1 guideline is widely perceived as a suboptimal approach, although currently without alternative [28] for estimating response (Table 29.1).

In a meta-analysis, overall RECIST1.1 response rate after neoadjuvant therapy were available for 61 studies [29], and pooled pathologic tumour destruction grades for 36 studies. Overall, the majority of patients were stable or in partial response on cross-sectional imaging (Table 29.2), and, upon available pathologic grading, most of the resected specimens showed minor to moderate histologic response (<50% tumour destruction, Table 29.3).

However, radiologic and pathologic grading are not correlated on a per-patient basis [30]. In a work-up of 38 specimens after NAT, all pathologic tumour

Table 29.1 RECIST1.1 definitions of imaging response

Category	RECIST1.1 classification
Complete response (CR)	No visible tumor
Partial response (PR)	≥30% decrease
Stable disease (SD)	Neither PR nor PD
Progressive disease (PD)	≥20% increase from best time point

Table 29.2 RECIST1.1 response rates on imaging after neoadjuvant therapy in a meta-analysis by Dhir et al. [29]

RECIST1.1 response rates after neoadjuvant therapy			
CR	PR	SD	PD
<1%	20%	59%	16%

Percentages display overall response rates from 61 studies; included are patients with resectable, borderline resectable and locally advanced PDAC

Table 29.3 Pathologic response from resected specimen in the same meta-analysis [29]

Pathologic overall response in resected specimen after neoadjuvant therapy					
Tumor destruction rate	<10%	10–50%	50–90%	<90%	No viable tumor
Frequencies (percentages)	12%	37%	27%	13%	3%

Table 29.4 Pathology-imaging correlation: Distribution of RECIST1.1 imaging response and pathologic tumor destruction grades in resected specimen, as found in the publication by Xia et al. [30]

	RECIST 1.1 response (n = 38)			
Pathologic tumor destruction grade	CR n = 1	PR n = 10	SD n = 26	PD n = 1
<50%		5	19	1
50–90%	1	3	4	
>90%		1	1	
No viable tumor		1	2	

destruction grades from minimal to complete were found in both radiologic partial responders and in patients with stable disease. Pathologic response of <50% tumour destruction was dominant in the largest RECIST group of stable disease. Of note there were three pathologic complete responders out of 38 specimens, two with RECIST stable disease, and one with partial response (Table 29.4).

In the light of unsatisfactory results of tumour re-assessment with RECIST1.1, alternative determinants of response are being investigated. In such, therapy-induced sharp tumour demarcation at the interface to normal pancreas parenchyma was found useful to predict improved survival, although the magnitude of the effect varied across cohorts [31].

29.4 Imaging Assessment of Resectability

29.4.1 Clinical Impact of Patient Selection Based on Imaging

The advent of novel neoadjuvant concepts has triggered extensive research on radiologic tumour changes after therapy, with special attention to resectability. Meta-analyses suggest high R0 rates in patients with borderline resectable PDAC: when 65% of patients were selected for surgery after FOLFIRINOX, R0 margins resulted in overall 89% of them. On an intention-to-treat basis, this translates into free margins in 58% of treated patients [25]. Selection for surgery becomes even more important in locally advanced PDAC with neoadjuvant therapy [32]: when an overall 28% of patients were brought to surgery after FOLFIRINOX, free margins were seen in 74% of operated subjects, resulting in only 22% of R0 margins on an intention-to-treat basis [33, 34]. Generally, imaging workup after neoadjuvant therapy reveals an overestimation of residual tumour burden around vessels and the

probability of R0 resection is difficult to estimate. Diagnostic accuracy for predicting resectability after neoadjuvant therapy yielded an accuracy of 58% in a publication by a French group [35].

29.4.2 Neoadjuvant Therapy and R0 Resection in Study Settings

The effect of FOLFIRINOX on resectability criteria, compared to pathologic margins, was presented in two initial publications with similar results.

In a first retrospective single-centre study of 40 patients after FOLFIRINOX (14 borderline resectable, 26 locally advanced), a strong trend towards surgical downstaging could be observed. But while 19 patients still remained radiographically in the locally advanced group, R0 margins could be achieved in 35/40 patients (92%), thus including a large portion of patients with persistent non-resectable disease on CT [36].

A French multicentre study [37] noted downstaging of resectability in only 6/36 patients after FOLFIRINOX, while the majority of patients remained stable on imaging. However, R0 resections were seen in 31 patients (86%), among them six patients with persistent locally advanced disease on imaging.

Subsequent publications confirmed, that resectability guidelines are not applicable on treated PDAC, since unchanged perivascular cuffs after neoadjuvant therapy are not correlated to resection margins [38] (Fig. 29.1).

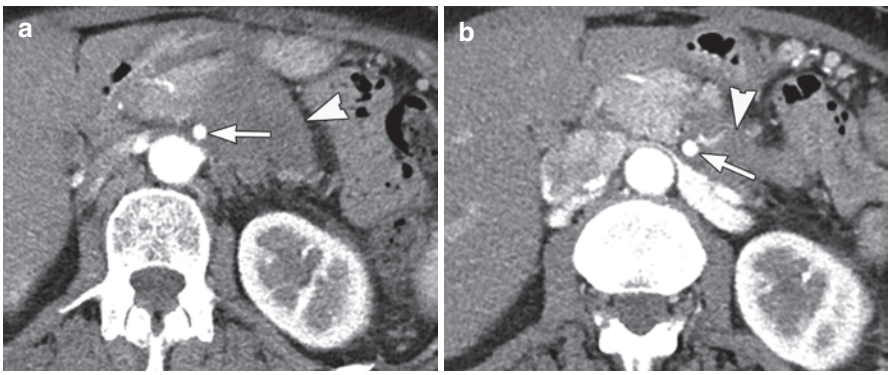

Fig. 29.1 Locally advanced PDAC under neo-adjuvant treatment. (**a**) Baseline image of a locally advanced PDAC in a 52-year-old female (arrowhead), with encasement of the superior mesenteric artery of >180° (arrow). (**b**) The same patient after neoadjuvant therapy with FOLFIRINOX. Considerable tumour shrinkage can be seen (arrowhead), however SMA encasement persists (arrow). The patient underwent total pancreatectomy with complete tumour dissection from the SMA and negative resection margins

29.4.3 Tested Predictors for Resectability and Survival After Neoadjuvant Therapy

Subsequently, several studies have focused on imaging predictors for margin-free surgery, with heterogeneous approaches and results.

29.4.3.1 Regression of Vessel Contact

A retrospective single-centre assessment of 47 patients found a regressive circumferential tumour contact with any of the crucial vessels (superior mesenteric vein, portal vein, superior mesenteric artery and celiac trunk) being predictive for R0 resections (PPV 91%). Specifically, a regression of circular SMA contact yielded an odds ratio of 3.82 (95% CI 1.27–11.5) for free margins [39]. Although a decrease in circumferential venous contact was also related to free margins, no correlation was observed between persistent narrowing of SMV/PV and R0 resection.

In a multicentre retrospective study on 36 patients [37], the circumferential decrease of perivascular cuffs did not reach significance levels when R0 and R1 resections were compared. However, patients with regressive encasement showed an advantage in disease-free survival, while the few patients with progressive encasement under therapy had significantly shorter disease-free survival.

29.4.3.2 Size and Resectability

Other studies published metric thresholds as predictors for negative margins. One of the largest single-institution retrospective studies with 141 patients found post-FOLFIRINOX differences in median size (2.3 cm vs. 3 cm) to be associated with attempted curative surgery (R0 in resected: 80%) [40]. Another publication revealed a 25 mm threshold after therapy, below which 78% of tumours had free margins [38]. Differences in size after treatment between R0 and R1 were observed in several publications (Table 29.5), but, using a linear correlation, post-treatment tumour

Table 29.5 Median/median tumor dimensions after neoadjuvant therapy and decrease in size, as reported in imaging studies after FOLFIRINOX

	Absolute dimension after neoadjuvant therapy (mm)		Size variability neoadjuvant therapy	
Study [Reference number]	R0	R1	R0	R1
Wagner et al. [37]	27	26	−65%	−56% (n.s.)
Marchegiani et al. [41]	21	26	−11 mm	−8 mm
Cassinotto et al. [39]	26	31	−7.6 mm	−7 mm
Michelakos et al. (median) [40]	23	30	−9 mm	0 mm

size was only weakly related to R0 margins [39]. There were considerable ranges of tumour sizes in tested populations both at baseline and post-treatment, consequently, dimensions associated with R0 or R1 resection are overlapping across studies. Noteworthy, the treatment-induced decrease in size was not significantly different between R0 and R1 patients (Table 29.5).

29.4.3.3 Tumour Enhancement

Increased enhancement under neoadjuvant therapy was observed in several studies and is attributed to fibrotic changes, similar to the delayed enhancement of myocardial infarcts in cardiac MRI or delayed enhancement of intrahepatic Cholangiocarcinoma, thought to represent fibrotic tumour components [41]. One retrospective single centre study found treatment-induced positive changes in enhancement in the venous phase being significantly higher in R0-resected tumours than in R1. However in other publications this treatment-effect was not significant [39] or even reversed with more pronounced density increases in R1 resected [37] (Table 29.6).

29.4.4 Study Characteristics of Imaging Predictor Assessment

In observational studies on PDAC morphology after therapy, patients proceeded to resection when they had stable disease or partial response on imaging. Imaging-progressive patients were excluded, and consequently, lack histological correlation. The decision to bring progressive patients to non-surgical palliation is based on high NPVs for assessing resectability in treatment naïve PDAC [41]. In an interesting aspect, one paper [40] reported two out of seven patients with post-treatment operability on CT, who eventually had non-resectable disease. This may suggest rare cases of underestimated local tumour extent.

Most publications are retrospective in design and, apart from the French [37] and Italian (three institutions) [38], all are single-centre.

Results of inter-observer concordance varied widely across publications, ranging from excellent in highly specialized centres [31] to only moderate κ-values of 0.57–0.58 [39]. In one publication, even the determination of a straightforward metric parameter, such as the longest axis, did not exceed a moderate κ-value of 0.54 among three radiologists with heterogeneous experience levels [38].

Table 29.6 Mean tumor enhancement (Hounsfield Units) before and after neoadjuvant therapy in R0 vs. R1 resected tumors

	Pre-treatment		Post-treatment	
Tumor enhancement during portal venous phase	R0	R1	R0	R1
Wagner et al. [37]	66	54	72	72
Marchegiani et al. [41]	62	65	78	68

Furthermore, resection margins of more than 1 mm were regularly used as a reference standard to evaluate the performance of cross-sectional imaging in treated PDAC. The histologic distribution of viable tumour within fibroinflammatory tissue has so far not been correlated to imaging on a lesion-by-lesion comparison.

29.5 Texture Analysis: Big Data Analysis in Imaging

29.5.1 Background

Radiomics, the mathematical exploitation of multiple background information contained in imaging data sets has gained momentum in recent years to quantitatively describe tumours before and after therapy. A most thriving application field of radiomics is CT/MR texture analysis to quantify visually non-perceptible heterogeneity [42, 43]. The method employs commercially available software to extract, on different complexity levels, quantitative descriptors such as distribution and statistical inter-relationship of grey levels from a Region of Interest (ROI). These input data are then processed to calculate parameters for quantifying tumour heterogeneity (Box 29.1). Validation of obtained output parameters (e.g. standard deviation of grey values, entropy, skewness, kurtosis, mean of the positive pixels) is performed by testing their association to histopathology and outcomes such as R0 resection or survival [44]. Descriptors may be derived from either CT, MRT or PET data sets.

Box 29.1 CT-Texture Analysis

CT Texture analysis is based on frequencies and inter-relationship of grey levels within an operator-determined Region of Interest (ROI, yellow circle). Input images first undergo pre-processing steps in order to selectively extract density features. Distribution and spatial variation of grey levels can be analysed using different models, with statistical-based models being most widely validated (Fig. 29.2a).

First order statistics describe grey-level frequencies, but do not refer to their spatial relationship. First order statistics are derived from intensity histograms representing grey level values on x-axis and their frequencies on y-axis. Histograms provide measures such as mean grey level (48 Hounsfield Units in this case), standard deviation and MPP (mean of positive pixels) to characterize a Region of Interest (Fig. 29.2b). Other first order statistics calculated from histograms are skewness (asymmetry of the histogram, left) and kurtosis (right, peakedness) compared to normal distribution. Energy (=uniformity, indicating how close the image is to a uniform Gaussian distribution) and first order entropy (irregularity of grey-level distribution in a histogram) are mathematically derived (Fig. 29.2c). Second-order statistics describe the spatial inter-relationship of intensities based on the probability of two or more pixel combinations in all directions (Fig. 29.2d).

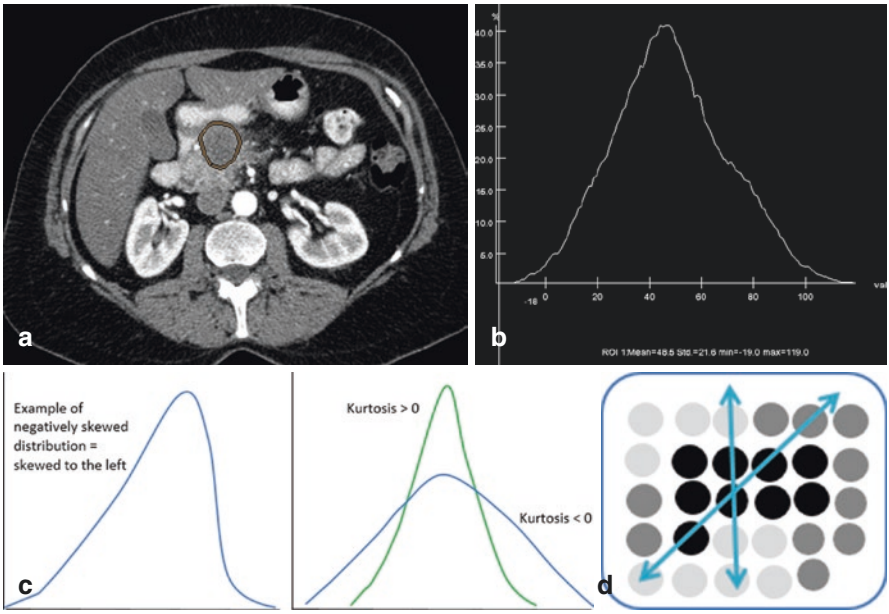

Fig. 29.2 (**a**–**d**) Principles of CT texture analysis

29.5.2 Application to Neoadjuvant Treatment of PDAC

Published data on the usefulness of CT Texture Analysis (CTTA) to estimate response in PDAC are preliminary. One group of investigators [45] tested a set of six CTTA parameters of 41 patients (mean grey-level intensity, entropy, mean of positive pixels, kurtosis, standard deviation, and skewness), together with tumour size and clinical variables in a multivariate regression model: two pre-treatment CTTA parameters, standard deviation and skewness were associated to survival. However, tumour size as a readily available parameter yielded higher significance levels than CTTA variables. In contrast to pre-treatment texture parameters, neither post-treatment values, nor their changes were associated to clinical outcomes.

Despite rapidly growing publication counts, radiomics need further standardization to provide inter-institutional reproducibility [44, 46]. Each step in the automated process is still dependent on variables, such as quality of input images, definition of parameters, robustness of extraction and statistical model building [47].

29.6 Functional Imaging: Diffusion-Weighted MRI for Monitoring Response

29.6.1 Current Application and Results

Diffusion-weighted MR imaging (DWI) offers functional tissue assessment by mapping the restriction of random (Brownian) molecule motion in water. Diffusion restriction is a marker for cellularity and pathologic characteristics of cellular barriers, both increased in tumours [48] (see also MR/MRCP for diagnosis and staging). Calculating apparent diffusion coefficients (ADC) in multiples of 10^{-3} mm^2/s from diffusion-weighted images allows for quantitative assessment of restricted diffusion. On ADC maps, low values—depicted as dark areas—represent restricted diffusion (Fig. 29.3). ADC maps are widely investigated in oncologic imaging to estimate response to neoadjuvant treatment [49, 50].

In an initial small study population of seven patients, pre-treatment ADC values were correlated to pathologic response grades [51]. However, in subsequent studies, the lack of technical standardization and methodologic variability proved challenging for quantifying robust thresholds of response. Two publications might demonstrate the heterogeneity of results with different techniques: in 2017, a single centre observation of 24 patients was performed on a 1.5 T unit with a b-value of 800 s/mm^2 [52]; in 2020 the same study group published a prospective assessment of 28 patients, using a 3 T MRI and a maximum b-value of 1000 s/mm^2 [53]. In the first study, a **pre-treatment** ADC value of $\geq 1.20 \times 10^{-3}$ mm^2/s was the strongest

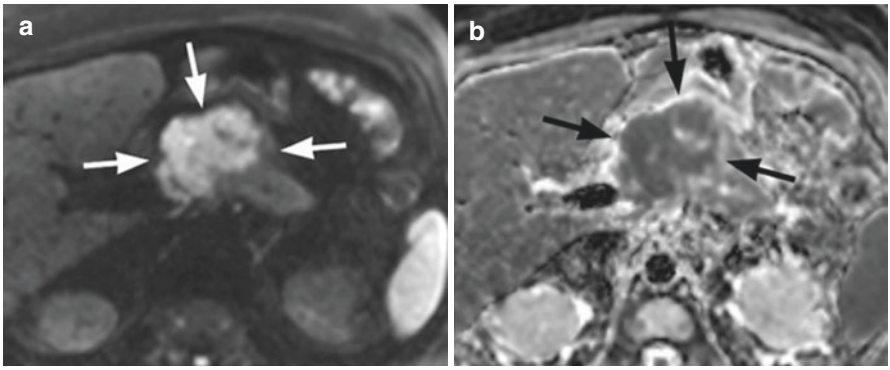

Fig. 29.3 Diffusion-weighted MR imaging. (**a**) Diffusion weighted image (DWI) of a PDAC at a b-value of 800 s/mm^2 reveals high signal intensities (arrows) as marker of restricted water diffusion within the tumour. The b-value describes intensity and time profile of the gradient pulse used. (**b**) Corresponding ADC map with predominantly low signal intensities (low ADC values) in the tumour area (arrows). Heterogeneity can also be noted

predictor for R0 resection (accuracy: 71%) and for pathologic response (accuracy: 83%; pathologic response defined as ≥30% tumour destruction). With 3 T MRI and b = 1000, the same parameter dropped in accuracy, but now **post-treatment** cut-off values of $\geq 1.40 \times 10^{-3}$ mm²/s emerged as strongest predictors: 75% accuracy for predicting R0 resection and 89% for histologic response. Additionally, patients with a post-treatment ADC of $\geq 1.40 \times 10^{-3}$ mm²/s had longer overall survival.

Another analysis of 23 patients with neoadjuvant therapy found an only moderate, although significant correlation of r = 0.517 (p = 0.02) between post-treatment ADC values and pathologic response grades [54]. Similar to prior studies, mean post-treatment ADC values were significantly higher, thus brighter than baseline values, and showed also an increase in standard deviation as a marker for supposed increasing tumour heterogeneity under therapy.

29.6.2 Tumour Heterogeneity, Definition of the Region of Interest and Future Developments

Assuming the concept of tumour heterogeneity, the definition of investigated tumour areas in terms of placing the Region of Interest (ROI) might explain the varying performance of pre- and post-treatment ADC values and ADC changes across papers. The selected ROI was either not described, encompassed the entire tumour volume, or was placed on one slice, with large vessels excluded.

The issue was addressed by another investigation with evaluation of both a selective ROI (the lowest ADC value, derived from the most diffusion-restricted area) and a ROI drawn over the entire tumour area, including necrosis. Both approaches used the slice with the largest tumour diameter [55] and only the relative change of ADC values under therapy was statistically evaluated. Not surprisingly, selective ADC values were more correlated to survival than whole-tumour-area ADC.

ADC values in a murine model with treated PDAC were inversely correlated to tumour "cellularity" [56]. This needs to be integrated with histopathologic knowledge of complex interactions between cellular stroma [19], inflammation and carcinoma cells. The differentiation of inflammation and adeno-carcinoma based on ADC values is still under debate and could be overcome by the generalized introduction of Intravoxel Incoherent Motion Diffusion-Weighted MRI (IVIM), a technique allowing for quantification of the fraction of flowing water in the microvasculature (perfusion fraction *f*, **see** Box 29.2) [57, 58]. In a preliminary work-up, the perfusion fraction was not useful to discriminate low/intermediate vs. high grade non-treated tumours [59], but a handful of papers confirmed the usefulness of IVIM for differentiating between PDAC and focal auto-immune

pancreatitis, owed to lower perfusion component in PDAC [60, 61]. Future investigation is needed to validate IVIM-DWI parameters for monitoring treatment response in PDAC [62].

Despite overlapping ADC values reported, there remains a strong consensus for routine application, that higher values ("brighter" ADC areas) are indicative for favourable tumour biology.

Similar to PET, requiring an interval of at least 4–5 weeks between NAT and restaging in order to allow restitution of actinic inflammation, MRI was performed within 3–5 weeks after completing NAT. Of note, in one publication MRI-ADC parameters outperformed the respective PET-SUV_{max} values [52].

Both functional methods may allow for estimating the overall response of a mass and predict survival [63], but they lack the spatial resolution to predict surgical margins around vessels. Still, in the light of evidence that pathologic response grade might be a factor associated with survival, biomarker imaging may play a role in future decision algorithms.

Box 29.2 IVIM (Intravoxel Incoherent Motion) MRI

IVIM imaging is a mathematical method to quantify all molecular motions contributing to a signal in Diffusion-weighted imaging (DWI). Apart from the molecular diffusion of water in tissue (true diffusion), water flowing in the capillary bed is the most important contributor to the signal, under the assumption of randomly orientated capillaries within a voxel (Fig. 29.4a). The signal component from water in the microvasculature is referred to as "pseudo-diffusion".

Different mathematical models have been proposed to separate true diffusion from microvascular blood flow [57, 58]. Using these algorithms, the contributing percentage of blood flow to a DWI signal and the perfusion fraction can be calculated and correlated to histology. Potential is seen e.g. in the quantification of neo-angiogenesis and monitoring of anti-angiogenetic drugs. Applications to pancreatic pathologies aimed at differentiating the poorly vascularized PDAC from atypical neuroendocrine neoplasms on imaging, or from focal auto-immune pancreatitis. IVIM-DW-MRI are prone to artefacts through image noise, respiratory and cardiac motion and to artefacts from gas in adjacent gastrointestinal structures.

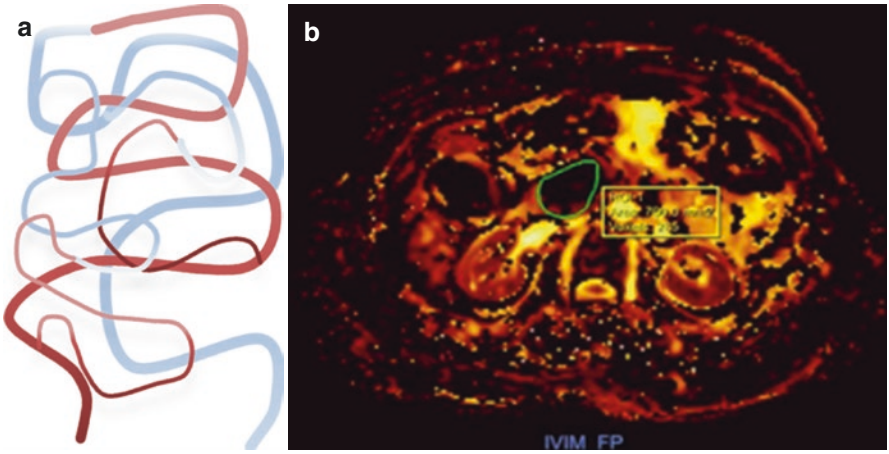

Fig. 29.4 Heterogeneous microvasculature in a tumour. (**a**) Randomly orientated capillaries within a voxel contribute to diffusion-weighted signals at lower b-values up to 600 s/mm^2 in the body. The effect becomes less important at high b-values. (**b**) IVIM perfusion fraction maps of a PDAC in the pancreatic head show a poorly vascularized lesion, encoded in dark colours. (From. De Robertis et al. [60])

29.7 Conclusion

The NCNN and ESMO panels currently endorse neoadjuvant therapy in borderline resectable PDAC [64, 65]. Several studies have shown that in a minority of patients, neoadjuvant therapy enabled R0 resection of locally advanced PDAC. However, histologic work-up suggests an inhomogeneous response of PDAC with interspersed carcinoma nests within stroma, extracellular matrix and inflammation. This poses a considerable challenge for interdisciplinary teams, to identify treated patients with potentially resectable disease.

According to current knowledge, RECIST1.1 partial response with radiologic mass regression occurs in a minority, while most patients remain stable on diagnostic imaging after neoadjuvant therapy. Generally, cross-sectional imaging overestimates the amount of residual viable tumour around vessels and thus cannot predict operability. There is no consistency across studies with regard to predictive imaging parameters for margin-free resection. Most studies are retrospective, single-centre, observational studies, examining changes in tumour size, vessel contact, or enhancement as hypotheses. Due to study heterogeneity, results are non-comparable, and statistical power is limited by small sample sizes. Though identification of potentially resectable patients is a rapidly evolving field in imaging research, at present, guidelines recommend taking patients to surgery after neoadjuvant therapy when there is no tumour progression on cross-sectional imaging [10, 66].

MR-DWI as a functional tool of MRI so far reveals conflicting results in the search for optimal threshold values of response. Also, while markers of low cellularity may be indicators of response, to date, functional imaging methods lack the spatial resolution to detect microscopic disease at the crucial interface of mass and vessel wall.

These limitations are thought to be overcome in the years ahead, and functional methods seems to harbour high potential for disease monitoring of treated pancreatic ductal adenocarcinoma.

References

1. Evans DB, George B, Tsai S. Non-metastatic pancreatic cancer: resectable, borderline resectable, and locally advanced-definitions of increasing importance for the optimal delivery of multimodality therapy. Ann Surg Oncol. 2015;22:3409–13.
2. Sugimoto M, Takahashi N, Farnell MB. Survival benefit of neoadjuvant therapy in patients with non-metastatic pancreatic ductal adenocarcinoma: a propensity matching and intention-to-treat analysis. J Surg Oncol. 2019;120:976.
3. Unno M, Hata T, Motoi F. Long-term outcome following neoadjuvant therapy for resectable and borderline resectable pancreatic cancer compared to upfront surgery: a meta-analysis of comparative studies by intention-to-treat analysis. Surg Today. 2019;49(4):295–9.
4. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206:833–46.
5. Sadot E, Doussot A, O'Reilly EM, Lowery MA, Goodman KA, Do RK, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol. 2015;22(11):3512–21.
6. Mokdad AA, Minter RM, Zhu H. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. J Clin Oncol. 2017;35(5):515–22.
7. Van Tienhoven GV, Versteijne E, Suker M, Groothuis KBC, Busch OR, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): a randomized, controlled, multicenter phase III trial. J Clin Oncol. 2018;36:LBA4002. https://doi.org/10.1200/JCO.2018.36.18_suppl.LBA4002.
8. Miyasaka Y, Ohtsuka T, Kimura R, Matsuda R, Mori Y, Nakata K, et al. Neoadjuvant chemotherapy with gemcitabine plus nab-paclitaxel for borderline resectable pancreatic cancer potentially improves survival and facilitates surgery. Ann Surg Oncol. 2019;26:1528–34.
9. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. Groupe Tumeurs Digestives of Unicancer, PRODIGE intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
10. Janssen QP, Buettner S, Suker M, Beumer BR, Addeo P, Bachellier P, et al. Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. J Natl Cancer Inst. 2019;111:782.
11. Schorn S, Demir IE, Reyes CM, Saricaoglu C, Samm N, Schirren R, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma - a systematic review and meta-analysis. Cancer Treat Rev. 2017;55:96–106.
12. Scheufele F, Hartmann D, Friess H. Treatment of pancreatic cancer - neoadjuvant treatment in borderline resectable/locally advanced pancreatic cancer. Transl Gastroenterol Hepatol. 2019;4:32.

13. Katz MH. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer. 2012;118(23):5749–56.
14. Isaji S, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18(1):2–11.
15. Siddiqui N, Vendrami CL, Chatterjee A, Miller FH. Advanced MR imaging techniques for pancreas imaging. Magn Reson Imaging Clin N Am. 2018;26(3):323–44.
16. Sasson AR, Wetherington RW, Hoffman JP, Ross EA, Cooper H, Meropol NJ, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: analysis of histopathology and outcome. Int J Gastrointest Cancer. 2003;34(2-3):121–8.
17. Evans DB, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg. 1992;127:1335–9.
18. Hartman DJ, Krasinskas AM. Assessing treatment effect in pancreatic cancer. Arch Pathol Lab Med. 2012;136(1):100–9.
19. Kalimuthu SN, Serra S, Dhani N, Chetty R, et al. The spectrum of histopathological changes encountered in pancreatectomy specimens after neoadjuvant chemoradiation, including subtle and less-well-recognised changes. J Clin Pathol. 2016;69:463–71.
20. Lafaro KJ, Melstrom LG. The paradoxical web of pancreatic cancer tumor microenvironment. Am J Pathol. 2019;189(1):44–57.
21. Sherman WH, Hecht E, Leung D, Chu K. Predictors of response and survival in locally advanced adenocarcinoma of the pancreas following neoadjuvant GTX with or without radiation therapy. Oncologist. 2018;23(1):4–e10.
22. Chatterjee D, Katz MH, Rashid A, Wang H, Iuga AC, Varadhachary GR, et al. Perineural and intraneural invasion in posttherapy pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. Am J Surg Pathol. 2012;36(3):409–17.
23. Chatterjee D, Rashid A, Wang H, Katz MH, Wolff RA, Varadhachary GR, et al. Tumor invasion of muscular vessels predicts poor prognosis in patients with pancreatic ductal adenocarcinoma who have received neoadjuvant therapy and pancreaticoduodenectomy. Am J Surg Pathol. 2012;36(4):552–9.
24. Naito Y, Ishikawa H, Sadashima E, Okabe Y, Takahashi K, Kawahara R, et al. Significance of neoadjuvant chemoradiotherapy for borderline resectable pancreatic head cancer: pathological local invasion and microvessel invasion analysis. Mol Clin Oncol. 2019;11(3):225–33.
25. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946–58.
26. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Pancreatology. 2016;16(1):28–37.
27. Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol. 2016;23(13):4352–60.
28. Baliyan V, Kordbacheh H, Parakh A, Kambadakone A, et al. Response assessment in pancreatic ductal adenocarcinoma: role of imaging. Abdom Radiol. 2018;43:435–44.
29. Dhir M, Malhotra GK, Sohal DPS, Hein NA, Smith LM, O'Reilly EM, et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. World J Surg Oncol. 2017;15(1):18.
30. Xia BT, Fu B, Wang J, Kim Y, Ahmad SA, Dhar VK, et al. Does radiologic response correlate to pathologic response in patients undergoing neoadjuvant therapy for borderline resectable pancreatic malignancy? J Surg Oncol. 2017;115(4):376–83.
31. Amer AM, Zaid M, Chaudhury B, Elganainy D, Lee Y, Wilke CT, et al. Imaging-based biomarkers: changes in the tumour interface of pancreatic ductal adenocarcinoma on computed tomography scans indicate response to cytotoxic therapy. Cancer. 2018;124(8):1701–9.

32. Del Chiaro M, Søreide K. Trials and tribulations of neoadjuvant therapy in pancreatic cancer. Br J Surg. 2018;105(11):1387–9.
33. Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas. 2015;44(4):515–21.
34. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17(6):801–10.
35. Cassinotto C, Cortade J, Belleannée G, Lapuyade B, Terrebonne E, Vendrely V, et al. An evaluation of the accuracy of CT when determining resectability of pancreatic head adenocarcinoma after neoadjuvant treatment. Eur J Radiol. 2013;82(4):589–93.
36. Ferrone C, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261:12–7.
37. Wagner M, Antunes C, Pietrasz D, Cassinotto C, Zappa M, Sa Cunha A, et al. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. Eur Radiol. 2017;27:3104–16.
38. Beleù A, Calabrese A, Rizzo G, Capelli P, Bellini N, Caloggero S. Preoperative imaging evaluation after downstaging of pancreatic ductal adenocarcinoma: a multi-center study. Cancers (Basel). 2019;11(2):E267. https://doi.org/10.3390/cancers11020267.
39. Cassinotto C, Mouries A, Lafourcade JP, Terrebonne E, Belleannée G, Blanc JF, et al. Locally advanced pancreatic adenocarcinoma: reassessment of response with CT after neoadjuvant CRT. Radiology. 2014;273(1):108–16.
40. Michelakos T, Pergolini I, Castillo CF, Honselmann KC, Cai L, Deshpande V. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2019;269(4):733–40.
41. Somers I, Bipat S. Contrast-enhanced CT in determining resectability in patients with pancreatic carcinoma: a meta-analysis of the positive predictive values of CT. Eur Radiol. 2017;27:3408–35.
42. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. Cancer Imaging. 2013;13:140–9.
43. Lubner MG, Stabo N, Lubner SJ, del Rio AM, Song C, Halberg RB, et al. CT textural analysis of hepatic metastatic colorectal cancer: pre-treatment tumour heterogeneity correlates with pathology and clinical outcomes. Abdom Imaging. 2015;40(7):2331–7.
44. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ, et al. CT texture analysis: definitions, applications, biologic correlates, and challenges. Radiographics. 2017;37(5):1483–503.
45. Cheng SH, Cheng YJ, Jin ZY, Xue HD, et al. Unresectable pancreatic ductal adenocarcinoma: role of CT quantitative imaging biomarkers for predicting outcomes of patients treated with chemotherapy. Eur J Radiol. 2019;113:188–97.
46. Summers RM. Texture analysis in radiology: does the emperor have no clothes? Abdom Radiol. 2017;42(2):342–5.
47. Yamashita R, Perrin T, Chakraborty J, Chou JF, Horvat N, Koszalka MA, et al. Radiomic feature reproducibility in contrast-enhanced CT of the pancreas is affected by variabilities in scan parameters and manual segmentation. Eur Radiol. 2019;30:195.
48. Thoeny HC, Ross BD. Predicting and monitoring cancer treatment response with DW-MRI. J Magn Reson Imaging. 2010;32(1):2–16.
49. Amodeo S, Rosman AS, Desiato V, et al. MRI-based apparent diffusion coefficient for predicting pathologic response of rectal cancer after neoadjuvant therapy: systematic review and meta-analysis. AJR Am J Roentgenol. 2018;211(5):W205–W16.
50. ACRIN 6698 Trial Team and I-SPY 2 Trial Investigators, Partridge SC, Zhang Z, Newitt DC, et al. Diffusion-weighted MRI findings predict pathologic response in neoadjuvant treatment of breast cancer: the ACRIN 6698 multicenter trial. Radiology. 2018;289(3):618–27.

51. Cuneo KC, Chenevert TL, Ben-Josef E, Feng MU, Greenson JK, Hussain HK, et al. A pilot study of diffusion-weighted MRI in patients undergoing neoadjuvant chemoradiation for pancreatic cancer. Transl Oncol. 2014;7:644–9.
52. Okada KI, Hirono S, Kawai M, Miyazawa M, Shimizu A, Kitahata Y, et al. Value of apparent diffusion coefficient prior to neoadjuvant therapy is a predictor of histologic response in patients with borderline resectable pancreatic carcinoma. J Hepatobil Pancreat Sci. 2017;24(3):161–8.
53. Okada KI, Kawai M, Hirono S, Kojima F, Tanioka K, Terada M, et al. Diffusion-weighted MRI predicts the histologic response for neoadjuvant therapy in patients with pancreatic cancer: a prospective study (DIFFERENT trial). Langenbeck's Arch Surg. 2020;405(1):23–33.
54. Dalah E, Erickson B, Oshima K, Feng MU, Greenson JK, Hussain HK, et al. Correlation of ADC with pathological treatment response for radiation therapy of pancreatic cancer. Transl Oncol. 2018;11(2):391–8.
55. Nishiofuku H, Tanaka T, Marugami N, Sho M, Akahori T, Nakajima Y, et al. Increased tumour ADC value during chemotherapy predicts improved survival in unresectable pancreatic cancer. Eur Radiol. 2016;26:1835–42.
56. Heid I, Steiger K, Trajkovic-Arsic M, Settles M, Eßwein MR, Erkan M, et al. Co-clinical assessment of tumor cellularity in pancreatic cancer. Clin Cancer Res. 2017;23(6):1461–70.
57. Iima M, Le Bihan D. Clinical intravoxel incoherent motion and diffusion MR imaging: past, present, and future. Radiology. 2016;278(1):13–32.
58. Le Bihan D. What can we see with IVIM MRI? NeuroImage. 2019;187:56–67.
59. Ma C, Li Y, Wang L, Wang Y, Zhang Y, Wang H, et al. Intravoxel incoherent motion DWI of the pancreatic adenocarcinomas: monoexponential and biexponential apparent diffusion parameters and histopathological correlations. Cancer Imaging. 2017;17(1):12.
60. De Robertis R, Cardobi N, Ortolani S, Tinazzi Martini P, Stemmer A, et al. Intravoxel incoherent motion diffusion-weighted MR imaging of solid pancreatic masses: reliability and usefulness for characterization. Abdom Radiol. 2019;44(1):131–9.
61. Klauss M, Lemke A, Grünberg K, Simon D, Re TJ, Wente MN, et al. Intravoxel incoherent motion MRI for the differentiation between mass forming chronic pancreatitis and pancreatic carcinoma. Investig Radiol. 2011;46(1):57–63.
62. Klaassen R, Gurney-Champion OJ, Engelbrecht MRW, Stoker J, Wilmink JW, Besselink MG, et al. Evaluation of six diffusion-weighted MRI models for assessing effects of neoadjuvant chemoradiation in pancreatic cancer patients. Int J Radiat Oncol Biol Phys. 2018;102(4):1052–62.
63. Kurosawa J, Tawada K, Mikata R, Ishihara T, Tsuyuguchi T, Saito M, et al. Prognostic relevance of apparent diffusion coefficient obtained by diffusion-weighted MRI in pancreatic cancer. J Magn Reson Imaging. 2015;42(6):1532–7.
64. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma. Version 2.2017. J Natl Compr Cancer Netw. 2017;15(8):1028–61.
65. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
66. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18(1):2–11.

Chapter 30
The Role of CA 19-9 in Pancreatic Adenocarcinoma

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Take Home Messages

- The epithelial cells—normal or tumoral—expressing CA 19-9 are not organ-specific but can be found in different tissues. CA 19-9 is therefore not specific of any specific malignant disease
- In pancreatic adenocarcinoma, CA 19-9 should not be used for screening
- In pancreatic adenocarcinoma, CA 19-9 is not validated for the diagnosis
- In pancreatic adenocarcinoma, CA 19-9 can be used as a prognostic marker, to assess resectability and treatment response

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Pearls and Pitfalls
- The normal CA 19-9 range in a healthy person is 0–37 units per milliliter.
- Obstructive cholestasis (intra- or extra-hepatic), either of benign or malignant etiology, may increase CA 19-9 value.
- In patients with a negative Lewis system, CA 19-9 is never detected in the blood. This situation is not uncommon, concerning 7–10% of the population
- In pancreatic adenocarcinoma and absence of cholestasis a value superior to 1000 U/ml should alert for distant metastases.
- After neoadjuvant treatment, a decrease in CA 19-9 after chemotherapy is associated with an increased survival
- Postoperative CA 19-9 value is also correlated to overall survival.

Future Perspectives
- It is unlikely that CA 19-9 will in the future become an interesting screening or diagnostic tool, even if he may help in some specific clinical situation. A better assessment as a prognostic marker will be interesting, especially in the setting of neoadjuvant treatment.

30.1 Introduction

Discovered by Koprowski et al. in colorectal cancer, carbohydrate antigen 19.9 (CA 19-9) is a ganglioside containing a sialyl-lacto-N-fucopentaose radical which is synthesized by epithelial cells [1]. The CA 19-9 epitope binds to a LEWIS group antigen (a, b) which circulates either free in plasma (or in other biological fluids such as pancreatic secretions) or is absorbed by erythrocytes. The concentration of this association (CA 19-9 epitope and antigen Lewis) is measurable in blood (Fig. 30.1). The epithelial cells expressing CA 19-9 are not organ-specific but can be found in different tissues such as the esophagus, the stomach, the bile ducts, the pancreas, the colon, the endometrium, the salivary glands, the kidney and the lung. Moreover, these cells may be part of healthy tissue as well as tumor tissue. CA 19-9 is therefore not specific of any specific malignant disease [2]. Regarding the pancreas, CA 19-9 is detectable in the pancreatic fluid (200–13,000 U/mL) and consequently inside pancreatic pseudocysts (800–116,000 U/mL).

30.1.1 Measuring CA 19-9 in Serum

In a blood sample, serum CA 19-9 level is usually estimated by using a sandwich-type immunoassay with electro chemiluminescence detection. The normal CA 19-9 range in a healthy person is 0–37 units per milliliter.

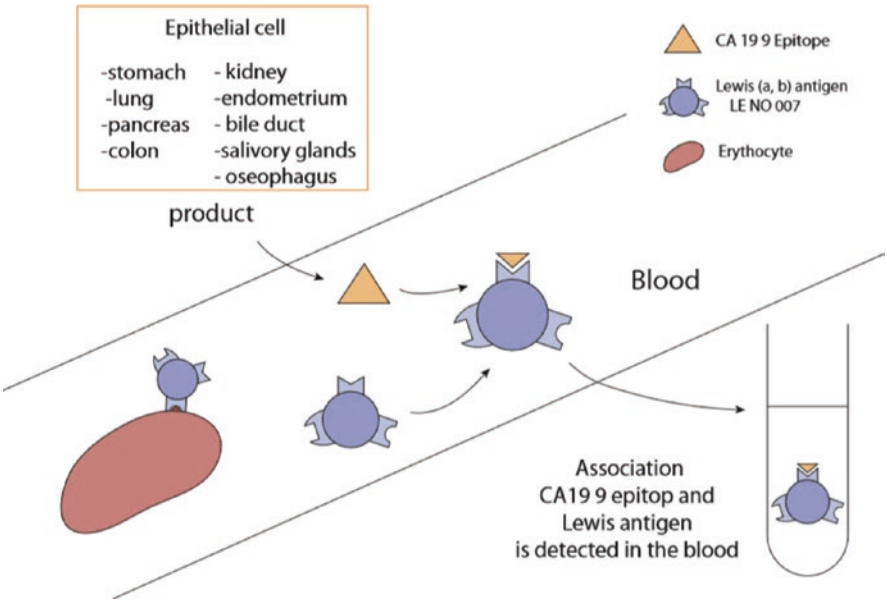

Fig. 30.1 CA19-9 in the blood

30.1.2 Malignancy

Steinberg et al. showed that CA 19-9 value is elevated in up to 70% of biliary tumors, 50% of hepatocellular carcinoma (with good positive predictive value when correlated with alpha-feto protein), 41% of gastric adenocarcinoma, 34% of colonic adenocarcinoma (with a good positive predictive value when correlated with carcinoembryonic antigen), 22% of esophageal adenocarcinoma and finally it can be found elevated in non-digestive tumors such as ovarian or pulmonary tumors (>15%) [3].

30.1.2.1 Benign Disease

Obstructive cholestasis (intra- or extra-hepatic), either of benign or malignant etiology, may increase CA 19-9 values (Table 30.1). There are two hypotheses explaining this phenomenon. The first one is related to local inflammation caused by obstruction, stimulating biliary epithelial cells ducts producing CA 19-9. The second one is related to obstruction induced biliary reflux which causes lesions of the biliary epithelium. This epithelial damage decreases the activity of a sialylglycoprotein receptors involved in the clearance of CA 19-9 and thus provokes its increase in the serum. The increase of CA 19-9 value is strongly correlated with the severity of jaundice. Hepatic cirrhosis increases CA 19-9 value in 62% of cases and chronic pancreatitis in up to 15–20% of cases [4, 5]. Little is known about CA 19-9

Table 30.1 Various causes of CA 19.9 value increase

Organ	Benign disease	Malignant disease
Pancreas	Acute and chronic pancreatitis	Pancreatic adenocarcinoma
Bile ducts	Cholangitis (e.g. primary biliary cholangitis, primary sclerosing cholangitis), obstructive cholestasis (e.g. gallstones, cystic fibrosis)	Cholangiocarcinoma
Stomach		Gastric adenocarcinoma
Colon		Colonic adenocarcinoma
Liver	Obstructive cholestasis Cirrhosis	Hepatocellular carcinoma
Esophagus		Esophageal adenocarcinoma
Ovaries		ovarian adenocarcinoma
Endometrium		endometrial adenocarcinoma
Lung	Pneumonia	Lung cancer
Other	Diabetes	

value elevation in diabetes. Studies show a correlation between CA 19-9 and HbA1c value or fasting plasma glucose [6, 7]. Thus, poorly controlled diabetes can be associated with increased values of CA 19-9. Two mechanisms explain this elevation. The first one is accelerated CA 19-9 biosynthesis due to an increased plasma and tissue glycosylation process owing to chronic hyperglycemia. The second one is increased CA 19-9 biosynthesis due to liver steatosis frequently associated with diabetes.

30.1.3 When Is CA 19-9 Not Detected?

In patients with a negative Lewis system, CA 19-9 is never detected in the blood. The Lewis antigen system is a blood group system based on antigens present in blood and other biological products either free or on the surface of erythrocytes. It is based upon two glycosyltransferases produced by two distinct genes (Lewis a and b) and producing three common phenotypes: Le(a+b-), Le(a-b+), and Le(a-b-). In patients with Lewis a-, b-type, the absence of gluconyltransferase does not allow association of the CA 19.9 epitope with the Lewis antigen and therefore their association cannot be measured [8, 9]. This situation is not uncommon, concerning 7–10% of the population and therefore CA 19-9 test sensitivity cannot exceed 90%.

30.2 Role of CA 19-9 in Pancreatic Adenocarcinoma

30.2.1 Screening

Several studies have shown that CA 19.9 has no place in mass screening for pancreatic cancer [10–12]. A Japanese study evaluated CA 19-9 in 5343 asymptomatic subjects. It was found abnormal in 385 (7.2%) of them with only two patients being diagnosed with pancreatic adenocarcinoma while 58 others being diagnosed with another cancer [13]. This marker was neither organ-specific nor specific of a malignant disease inducing a high false positive rate in the population, as well as a low positive predictive value given an optimal sensitivity. The positive predictive value for a CA 19-9 threshold of 37 IU/mL, 100 IU/mL, 300 IU/mL or 1000 IU/mL was 0.04%, 0.35%, 0.5% and 2%, respectively. This clearly shows that using CA 19-9 in the detection of adenocarcinoma in the general population would have a low cost-benefit ratio since for 10,000 measurements, we would averagely get four true positive diagnoses and 1000 false positive ones.

Targeted measurement of CA 19-9 value is also of no interest. The same Japanese study showed that out of 12,840 asymptomatic patients and 8706 patients with symptoms consistent with pancreatic cancer, 18 cancers were identified in the first group while only four cancers were identified in the second [13]. Moreover, taking into account that targeted populations with risk factors for pancreatic adenocarcinoma, such as diabetes or chronic pancreatitis, independently elevate CA 19-9 values could decrease even more diagnostic specificity of this marker. However, Zubarik et al. showed that CA 19-9 screening of high-risk individuals (patients with a family history of pancreatic cancer, hereditary pancreatitis and Peutz-Jeghers syndrome) seems to be of interest [14]. A total of 546 subjects were screened in this study of which 27 patients had elevated CA19-9 values out of which five patients were detected with a neoplastic lesion and one patient with a pancreatic adenocarcinoma. Further studies need however to be performed in order to evaluate the cost-benefit ratio of CA 19-9 as a screening tool.

30.2.2 Diagnosis of PDAC or Precursors

30.2.2.1 Intraductal Papillary Mucinous Neoplasm of the Pancreas (IPMN)

Very few studies had assessed CA 19-9 in IPMN, and its dosage has no value in diagnosis. Nevertheless, European and International guideline recommend dosage of CA 19-9, since its elevation is considered as a worrisome feature or a relative surgical indication.

30.2.2.2 Pancreatic Adenocarcinoma

Elevated CA 19-9 value has not been validated for the diagnosis of pancreatic adenocarcinoma [11, 15]. Limits on its measurement is its lack of specificity due to many false positive results and its lack of sensitivity since it does not exceed 90% (cf. patients with Lewis (a-, b-)). It should not be used as a diagnostic tool in routine clinical practice.

However, CA 19-9 can be a useful diagnostic tool in difficult situations as already published by some authors. Sensitivity of CA 19-9 is dependent on the tumor's size [16–18]. For tumors less than 2 cm in diameter the CA 19-9 is of no diagnostic interest, however, for tumors over 3 cm an increasing positive correlation has been observed. Overall, CA 19-9 is abnormal in 50% of patients with non-metastatic disease.

It has also been shown that CA 19-9 serum level is higher when comparing malignant to benign disease [19]. Discovery of a pancreatic mass associated with a CA 19-9 value superior to 300 U/mL should generate suspicion for malignant disease [20]. Other studies have shown that after successfully drained obstructive jaundice, persistent CA 19-9 serum levels are indicative of pancreatic adenocarcinoma [21]. Marrelli et al. [22] have shown that CA 19-9 serum levels over 90 U/mL 1 week after endoscopic biliary drainage are strongly indicative of a malignant cause. Moreover, a CA 19-9 cut off value might help tailoring patient's management. Indeed, a CA 19-9 level greater than 1000 U/mL is associated with a significant risk of metastatic disease [11, 23].

Finally, many studies have investigated combining other tumor markers with CA 19.9 (ACE, albumin, etc.) in the diagnosis of pancreatic adenocarcinoma, but none has found a sufficiently sensitive and specific score to be clinically useful [24–28].

30.3 Prognostic Assessment

30.3.1 Resectability Assessment

The CA 19-9 value may help in the decision of resectability of a pancreatic tumor. One study showed a correlation between CA 19-9 value and tumor grade [29]. In 114 patients with pancreatic adenocarcinoma with 72 patients undergoing surgery, stage Ia presented an average CA 19-9 value of 40.04 U/ml, significantly lower than stage IIA which was 469.64 U/ml, stage IIB at 747.79 U/ml, stage III at 709 U/ml and stage IV at 3239 U/ml. Many publications have sought different value cut-offs predicting respectability without ever really agreeing. Overall, it seems that CA 19-9 value >300 U/mL should raise suspicion of non-resectability most often being true for values >1000 U/mL. Hartwig et al. showed that CA19-9 is a significant predicting factor of resectability, with 80% of patients being resectable for CA 19-9 values <250 U/mL [30]. However, none of these studies compares the CA 19-9 value with imaging or endoscopic ultrasound data currently used to define tumor

resectability [31]. It should also be noted that CA 19-9 does not provide any information on tumor's vascular relationship. In 8–15% of cases of resectable pancreatic adenocarcinomas liver metastases or carcinomatosis is discovered only intraoperatively. Thus, the only clinical benefit of this marker could be a value superior to 1000 U/ml and should alert the surgeon in carefully searching for distant metastases before surgery [32–34].

30.3.2 Assessment of Treatment Response

30.3.2.1 After Neoadjuvant Treatment

The use of CA 19-9 in evaluating the response to chemotherapy in pancreatic adenocarcinoma is promising [35, 36]. Aoki et al. demonstrated in 240 patients who had had neoadjuvant chemotherapy that a decrease in CA 19.9 value over 103 IU/ml correlated with a decreased risk of hepatic recurrence [37]. Many studies have evaluated CA 19-9's correlation to survival with heterogenous results but it seems that a decrease in CA 19-9 after chemotherapy is associated with an increased survival [38, 39]. Recently, a study has shown that using a cut-off of 30% decrease in CA19-9 value, 9/10 patients were correctly classified as resectable [40].

30.3.2.2 After Surgical Resection

Hata et al. showed in 269 patients with resected pancreatic adenocarcinoma that patients with elevated postoperative CA19-9 levels had a higher rate of microscopically positive resection margins, hepatic or peritoneal recurrence [39, 41]. Elevation of the CA 19-9 value precedes the radiological visualization of a recurrence by 6 months in average [42]. Thus, CA 19-9 surveillance can facilitate early detection of recurrence. The impact of such a strategy on overall survival has however still not been studied. It should be remembered, however, that postoperative CA19-9 elevation might be related to a benign etiology. As such, it can be postoperative cholangitis or obstructive jaundice due to anastomotic stenosis or an intrahepatic abscess.

Postoperative CA 19-9 value is also correlated to overall survival [39, 43]. Postoperative value normalization is related to survival time from 17 to 22 months against 5–9 months if the value is maintained high [23, 30, 41, 44]. Moreover, postoperative CA 19-9 values <200 U/mL are correlated with longer survival [45]. T. Sakamoto et al. in a group of 103 patients demonstrated that combining measurement of preoperative CA 19-9 and platelet to lymphocyte ratio (PLR) is a useful predicting factor for resected adenocarcinomas. High CA 19-9 and PLR indicate a poor prognosis in overall and disease-free survival [46, 47]. Overall, the clinical utility of CA19-9 for postoperative monitoring is still unclear but seems that surveillance of postoperative CA 19-9 values is still a valuable tool.

Table 30.2 Clinical value of CA19-9 in the management of pancreatic cancer

Stage in management	Value	Role
Screening	+/−	Unsuitable for general population screening
		May have a role in high-risk groups
Diagnosis	++	May be used as an adjuvant marker to other investigations
Predicting resectability	+	Valuable indicator of tumor burden
		The tumor marker alone is unable to determine anatomical margins
Perioperative prognostic value	+++	High preoperative levels correlate with poor postoperative prognosis
		Persistent postoperative elevated values are associated with poor outcomes.
Predicting response to chemotherapy	+	Heterogeneity in therapeutic regimes limit the ability for accurate prediction of response to treatment
		Post-treatment decreasing value is an indicator of increased survival
Postoperative surveillance	++	Increase may precede radiological recurrence up to 6 months
		Institution dependent and may have a role in surveillance
		3–6 month surveillance for the first year, then annual surveillance

30.3.3 Role of CA 19-9 in Metastatic Pancreatic Cancer

Pre-chemotherapy CA 19-9 is not predictive of tumor response to chemotherapy [48]. In patients with unresectable pancreatic adenocarcinoma CA 19-9 appears to be a good indicator of survival [49]. Average overall survival is 10–20 months for values below 420 U/mL, compared to 7–8 months for values greater than 1000 U/mL [50–52]. CA 19-9 is also correlated to survival rates for patients treated with radiochemotherapy. Decreasing values of CA 19-9 during treatment are correlated to an average survival up to 5–14 months compared to 3–8 months for those with persisting high values of CA 19-9 [53, 54]. As expected, for patients with progressing tumors additional information provided by CA 19-9 value is weak. Finally, CA 19-9 value is not correlated to the quality of life [55]. A summary of CA 19-9's clinical value in the management of pancreatic adenocarcinoma is provided in Table 30.2.

30.4 Conclusions

- In pancreatic adenocarcinoma, CA 19-9 should not be used for screening and is not validated for diagnosis, nevertheless, CA 19-9 can be used as a prognostic marker, to assess resectability and treatment response, especially after neoadjuvant treatment. It is important to know that obstructive cholestasis (intra- or extra-hepatic), either of benign or malignant etiology, may increase CA 19-9

value, and that in patients with a negative Lewis system, CA 19-9 is never detected in the blood. This situation is not uncommon, concerning 7–10% of the population

References

1. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. Som Cell Genet. 1979;5(6):957–71.
2. Pavai S, Yap SF. The clinical significance of elevated levels of serum CA 19-9. Med J Malaysia. 2003;58(5):667–72.
3. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol. 1990;85(4):350–5.
4. Van Heerde MJ, Buijs J, Hansen BE, de Waart M, van Eijck CHJ, Kazemier G, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. Dig Dis Sci. 2014;59(6):1322–9.
5. Chang M-C, Liang P-C, Jan S, Yang C-Y, Tien Y-W, Wei S-C, et al. Increase diagnostic accuracy in differentiating focal type autoimmune pancreatitis from pancreatic cancer with combined serum IgG4 and CA19-9 levels. Pancreatology. 2014;14(5):366–72.
6. Aoki Y, Yanagisawa Y, Ohfusa H, Kawa S, Oguchi H, Furuta S. Elevation of serum CA 19-9 in parallel with HbA1c in a diabetic female with the Lewis(a+b-) blood group. Diabetes Res Clin Pract. 1991;13(1-2):77–81.
7. Nakamura N, Aoji O, Yoshikawa T, Mori K, Kajiyama S, Kitagawa Y, et al. Elevated serum CA19-9 levels in poorly controlled diabetic patients. Jpn J Med. 1986;25(3):278–80.
8. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res. 1987;47(20):5501–3.
9. Vestergaard EM, Hein HO, Meyer H, Grunnet N, Jørgensen J, Wolf H, et al. Reference values and biological variation for tumor marker CA 19-9 in serum for different Lewis and secretor genotypes and evaluation of secretor and Lewis genotyping in a Caucasian population. Clin Chem. 1999;45(1):54–61.
10. Homma T, Tsuchiya R. The study of the mass screening of persons without symptoms and of the screening of outpatients with gastrointestinal complaints or icterus for pancreatic cancer in Japan, using CA19-9 and elastase-1 or ultrasonography. Int J Pancreatol. 1991;9:119–24.
11. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105–19.
12. Kim J-E, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol. 2004;19(2):182–6.
13. Chang C-Y, Huang S-P, Chiu H-M, Lee Y-C, Chen M-F, Lin J-T. Low efficacy of serum levels of CA 19-9 in prediction of malignant diseases in asymptomatic population in Taiwan. Hepato-Gastroenterology. 2006;53(67):1–4.
14. Zubarik R, Gordon SR, Lidofsky SD, Anderson SR, Pipas JM, Badger G, et al. Screening for pancreatic cancer in a high-risk population with serum CA 19-9 and targeted EUS: a feasibility study. Gastrointest Endosc. 2011;74(1):87–95.
15. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33(3):266–70.
16. Iishi H, Yamamura H, Tatsuta M, Okuda S, Kitamura T. Value of ultrasonographic examination combined with measurement of serum tumor markers in the diagnosis of pancreatic cancer of less than 3 cm in diameter. Cancer. 1986;57(10):1947–51.

17. Malesci A, Montorsi M, Mariani A, Santambrogio R, Bonato C, Bissi O, et al. Clinical utility of the serum CA 19-9 test for diagnosing pancreatic carcinoma in symptomatic patients: a prospective study. Pancreas. 1992;7(4):497–502.
18. Satake K, Chung YS, Umeyama K, Takeuchi T, Kim YS. The possibility of diagnosing small pancreatic cancer (less than 4.0 cm) by measuring various serum tumor markers. A retrospective study. Cancer. 1991;68(1):149–52.
19. Morris-Stiff G, Teli M, Jardine N, Puntis MC. CA19-9 antigen levels can distinguish between benign and malignant pancreaticobiliary disease. Hepatobil Pancreat Dis Int HBPD INT. 2009;8(6):620–6.
20. Kim HJ, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, et al. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. Am J Gastroenterol. 1999;94(7):1941–6.
21. Benamouzig R, Buffet C, Fourre C, Ink O, Moati F, Etienne JP. Serum levels of carbohydrate antigenic determinant (CA 19.9) in obstructive jaundice. Dig Dis Sci. 1989;34(10):1640–2.
22. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg. 2009;198(3):333–9.
23. Rudnicki J, Agrawal AK, Grzebieniak Z, Zukrowski P, Zyśko D, Jelen M, et al. Prognostic value of CA 19-9 level in resectable pancreatic adenocarcinoma. Folia Histochem Cytobiol. 2010;48(2):249–61.
24. Ferri MJ, Saez M, Figueras J, Fort E, Sabat M, López-Ben S, et al. Improved pancreatic adenocarcinoma diagnosis in jaundiced and non-jaundiced pancreatic adenocarcinoma patients through the combination of routine clinical markers associated to pancreatic adenocarcinoma pathophysiology. PLoS One. 2016;11(1):e0147214.
25. Liu J, Gao J, Du Y, Li Z, Ren Y, Gu J, et al. Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. Int J Cancer. 2012;131(3):683–91.
26. Sivarman A, Muthukrishnan A, Boopathy Senguttvan N, Anil Suchak S, Kannan U. Predictors of malignancy in pancreatic head mass: a prospective study. Pan Afr Med J. 2011;9:30. Accessed 9 Sept 2019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3215552/.
27. Zhang Y, Yang J, Li H, Wu Y, Zhang H, Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. Int J Clin Exp Med. 2015;8(7):11683–91.
28. Hasan S, Jacob R, Manne U, Paluri R. Advances in pancreatic cancer biomarkers. Oncol Rev. 2019;13(1):410.
29. Kim YC, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Can preoperative CA19-9 and CEA levels predict the resectability of patients with pancreatic adenocarcinoma? J Gastroenterol Hepatol. 2009;24(12):1869–75.
30. Hartwig W, Strobel O, Hinz U, Fritz S, Hackert T, Roth C, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. Ann Surg Oncol. 2013;20(7):2188–96.
31. Hartwig W, Hackert T, Hinz U, Gluth A, Bergmann F, Strobel O, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. Ann Surg. 2011;254(2):311–9.
32. Alexakis N, Gomatos IP, Sbarounis S, Toutouzas K, Katsaragakis S, Zografos G, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. Eur J Surg Oncol. 2015;41(2):265–9.
33. Takahashi H, Ohigashi H, Ishikawa O, Eguchi H, Gotoh K, Yamada T, et al. Serum CA19-9 alterations during preoperative gemcitabine-based chemoradiation therapy for resectable invasive ductal carcinoma of the pancreas as an indicator for therapeutic selection and survival. Ann Surg. 2010;251(3):461–9.
34. Maithel SK, Maloney S, Winston C, Gönen M, D'Angelica MI, Dematteo RP, et al. Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2008;15(12):3512–20.

35. Heger U, Sun H, Hinz U, Klaiber U, Tanaka M, Liu B, Sachsenmaier M, et al. Induction chemotherapy in pancreatic cancer: CA 19-9 may predict resectability and survival. HPB (Oxford). 2019;22:224. pii: S1365-182X (19)30599-4.
36. Perri G, Prakash L, Wang H, Bhosale P, Varadhachary GR, Wolff R, et al. Radiographic and serologic predictors of pathologic major response to preoperative therapy for pancreatic cancer. Ann Surg. 2019; https://doi.org/10.1097/SLA.0000000000003442.
37. Aoki S, Motoi F, Murakami Y, Sho M, Satoi S, Honda G, et al. Decreased serum carbohydrate antigen 19-9 levels after neoadjuvant therapy predict a better prognosis for patients with pancreatic adenocarcinoma: a multicenter case-control study of 240 patients. BMC Cancer. 2019;19(1):252.
38. Boone BA, Steve J, Zenati MS, Hogg ME, Singhi AD, Bartlett DL, et al. Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. Ann Surg Oncol. 2014;21(13):4351–8.
39. Hata S, Sakamoto Y, Yamamoto Y, Nara S, Esaki M, Shimada K, et al. Prognostic impact of postoperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol. 2012;19(2):636–41.
40. van Veldhuisen E, Vogel JA, Klompmaker S, Busch OR, van Laarhoven HWM, van Lienden KP, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB. 2018;20(7):605–11.
41. Takagi C, Kikuchi Y, Shirakawa H, Hoshimoto S, Tomikawa M, Ozawa I, et al. Predictive factors for elevated postoperative carbohydrate antigen 19-9 levels in patients with resected pancreatic cancer. Anticancer Res. 2019;39(6):3177–83.
42. Rieser CJ, Zenati M, Hamad A, Al Abbas AI, Bahary N, Zureikat AH, et al. CA19-9 on postoperative surveillance in pancreatic ductal adenocarcinoma: predicting recurrence and changing prognosis over time. Ann Surg Oncol. 2018;25(12):3483–91.
43. Kondo N, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol. 2010;17(9):2321–9.
44. Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol. 2012;23(7):1713–22.
45. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2006;24(18):2897–902.
46. Sakamoto T, Saito H, Amisaki M, Tokuyasu N, Honjo S, Fujiwara Y. Combined preoperative platelet-to-lymphocyte ratio and serum carbohydrate antigen 19-9 level as a prognostic factor in patients with resected pancreatic cancer. Hepatobil Pancreat Dis Int HBPD INT. 2019;18(3):278–84.
47. Negoi I, Beuran M, Hostiuc S, El-Hussuna A, de Madaria E. Platelet-to-lymphocyte ratio and CA19-9 are simple and informative prognostic factors in patients with resected pancreatic cancer. Hepatobil Pancreat Dis Int HBPD INT. 2019;18(3):203–5.
48. Hess V, Glimelius B, Grawe P, Dietrich D, Bodoky G, Ruhstaller T, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. Lancet Oncol. 2008;9(2):132–8.
49. Usón Junior PLS, Callegaro-Filho D, Bugano DDG, Moura F, Maluf FC. Predictive value of serum carbohydrate antigen 19-9 (CA19-9) for early mortality in advanced pancreatic cancer. J Gastrointest Cancer. 2018;49(4):481–6.
50. Katz A, Hanlon A, Lanciano R, Hoffman J, Coia L. Prognostic value of CA 19-9 levels in patients with carcinoma of the pancreas treated with radiotherapy. Int J Radiat Oncol Biol Phys. 1998;41(2):393–6.
51. Ikeda M, Okada S, Tokuuye K, Ueno H, Okusaka T. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. Cancer. 2001;91(3):490–5.

52. Micke O, Bruns F, Kurowski R, Horst E, de Vries AF, Hausler JW, et al. Predictive value of carbohydrate antigen 19-9 in pancreatic cancer treated with radiochemotherapy. Int J Radiat Oncol Biol Phys. 2003;57(1):90–7.
53. Saad ED, Machado MC, Wajsbrot D, Abramoff R, Hoff PM, Tabacof J, et al. Pretreatment CA 19-9 level as a prognostic factor in patients with advanced pancreatic cancer treated with gemcitabine. Int J Gastrointest Cancer. 2002;32:35–41.
54. Diaz CL, Cinar P, Hwang J, Ko AH, Tempero MA. CA 19-9 response: a surrogate to predict survival in patients with metastatic pancreatic adenocarcinoma. Am J Clin Oncol. 2019;42(12):898–902.
55. Bernhard J, Dietrich D, Glimelius B, Hess V, Bodoky G, Scheithauer W, et al. Estimating prognosis and palliation based on tumour marker CA 19-9 and quality of life indicators in patients with advanced pancreatic cancer receiving chemotherapy. Br J Cancer. 2010;103(9):1318–24.

Chapter 31
Biomarkers in Pancreatic Cancer

Daniel Ansari and Roland Andersson

Take Home Messages

- CA 19-9 remains the only approved serum marker for pancreatic cancer.
- Testing for microsatellite instability-high (MSI-high)/deficient mismatch repair (dMMR) has been approved for stratifying patients to pembrolizumab treatment.
- Testing for BRCA1/2 mutations has been approved for selecting patients to olaparib.
- Novel investigational biomarkers, including genetic markers, microRNAs, as well as proteins have been identified for diagnostic, prognostic or predictive purposes.
- Combinations of biomarkers may provide more discriminatory power than a single biomarker.
- Further efforts are needed to validate novel biomarkers in larger, prospective clinical trials.

Pearls and Pitfalls

- Improvements in the depth and throughput of genomics and proteomics technologies have facilitated the discovery of novel biomarkers for pancreatic cancer.
- However, precision medicine is difficult to obtain through genomics or proteomics alone.

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- To overcome this challenge, methods have been developed for combining genomics information with sample-specific proteomics information.
- Proteogenomics integrates genome, transcriptome and proteome data, enabling new insights due to a more complete and unified understanding of complex biological processes.
- The use of proteogenomics may aid in creating a true understanding of disease biology and the identification of more precise biomarkers for diagnosis and predicting drug sensitivity.

Future Perspectives

- The identification of reproducible and validated biomarkers of clinical utility is a major step toward improving outcomes in patients with pancreatic cancer.
- Novel clinical trial designs that integrate biomarker analyses and companion diagnostics need to be developed.
- In the future, all patients with pancreatic cancer may receive comprehensive proteogenomics profiling of their tumors, as a complement to standard histopathological evaluation, in order to select specific molecular therapy.

31.1 Introduction

Biomarker research is a rapidly expanding field fueled by technological advances in high-throughput omics technologies and analytical tools, as well as by an unmet need in clinical medicine for better stratification tools. For many solid tumors, biomarkers are now routinely used for treatment selection. Examples include lung cancer (EGFR mutations, ALK and ROS1 gene rearrangements, BRAF V600E mutations) [1], malignant melanoma (BRAF V600E mutations) [2], and breast cancer (ER, PgR and HER2) [3]. Immune checkpoint inhibitors are guided by measurement of PD-L1, as well as microsatellite instability-high (MSI-high)/deficient mismatch repair (dMMR), in a range of solid tumors [4, 5].

Pancreatic cancer has the lowest survival rate of any major organ cancer [6]. Despite much research, there is a lack of clinically validated biomarkers for this tumor type. Blood contains huge amounts of potentially diagnostic information and circulating biomarkers may lead to earlier and more accurate diagnosis of pancreatic tumors. Serum carbohydrate antigen (CA) 19-9 is the only routinely used serum biomarker for pancreatic cancer. However, inadequate sensitivity and specificity limits the application of CA 19-9 as a screening tool, and CA 19-9 can only be recommended for disease monitoring [7].

Genome sequencing studies have highlighted specific molecular events in pancreatic cancer including DNA mutations, chromosomal rearrangements and gene amplifications [8–13]. Many of the identified oncogenes are “druggable” enabling

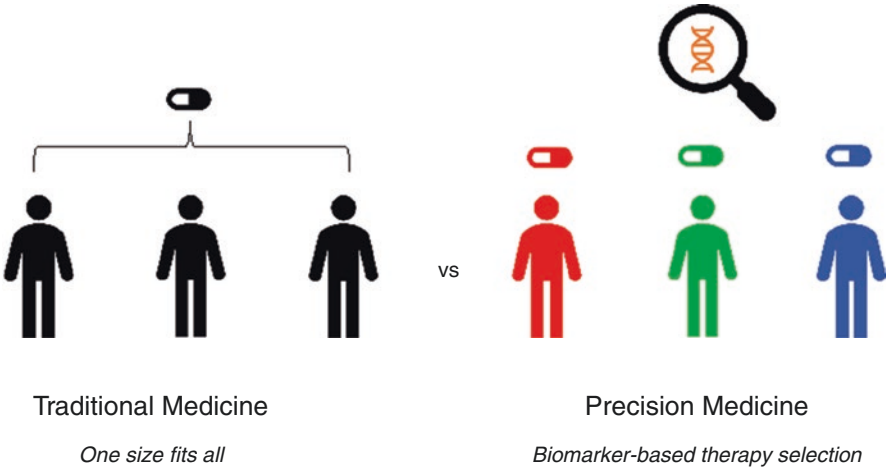

Fig. 31.1 Traditional medicine versus biomarker-driven precision medicine

development of novel anti-tumor therapies. Genomic and transcriptomic data have also helped define subgroups of pancreatic cancer with distinct tumor biology that require subtype-specific treatment [9, 11, 13]. The "one size fits all" strategy is no longer relevant, and we have now entered the era of "precision medicine" or "biomarker-driven cancer therapy" (Fig. 31.1) [14]. Novel precision oncology trial designs have been developed using "master protocols", including "basket trials", "umbrella trials" and "platform trials", in order to more effectively evaluate new anti-cancer therapies [15]. "Basket trials" evaluate targeted therapies in multiple diseases that share similar molecular alterations. By contrast, "umbrella trials" investigate multiple targeted therapies in a single disease that is stratified into molecular subgroups. "Platform trials" evaluate multiple interventions in a disease in a perpetual manner, with interventions entering and leaving the platform based on pre-defined criteria. Many tissue biomarkers are emerging in pancreatic cancer with the potential to influence therapy selection. Pembrolizumab is the first FDA approved biomarker-based therapy for pancreatic cancer, which is indicated in MSI-high/dMMR malignancies agnostic of organ of origin [16]. Recently, the FDA approved PARP inhibitor olaparib in metastatic pancreatic cancer and BRCA1/2 testing was approved as companion diagnostic test [17].

For precision medicine to be realized, it is essential to develop high quality biomarkers. However, the implementation of new biomarkers is a long and arduous process, involving discovery, validation, regulatory approval, and commercialization. The inability to demonstrate clinical utility is the most common reason for investigational biomarkers failing to be translated to the clinic [18]. To address this problem, clinical utility data need be collected early and samples need to reflect the clinical question raised. In this chapter, we discuss recent progress in biomarkers for pancreatic cancer and focus on their clinical utility for early detection, prognostication and prediction of treatment response.

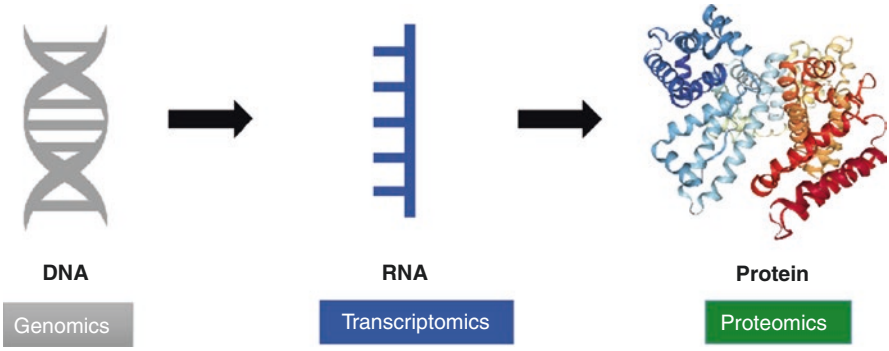

Fig. 31.2 The relationship between genomics, transcriptomics and proteomics

31.2 The Biomarker Definition

The National Institutes of Health (NIH) defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention" [19]. Biomarkers may be genes, RNA, proteins or metabolites (Fig. 31.2), and they may be identified through global profiling studies or targeted approaches. They can be measured in tissue, as well as body fluids such as blood, urine, saliva and cyst fluid. Tissue has the highest concentration of tumor biomarkers. One sound strategy is to first look for biomarkers in cancer tissue and then search for the cancer-derived biomarkers in biofluids, such as blood.

Quantitative imaging features may also be considered as biomarkers according to the NIH definition. "Radiomics" refers to the collection, processing and analysis of a large amount of high-dimensional imaging data. "Radiomics" has been applied for differentiating between high-risk and low-risk intraductal papillary mucinous neoplasms (IPMN) [20], as well as for building prognostic models in patients with pancreatic cancer [21].

31.3 Technologies for Biomarker Discovery

The development next-generation sequencing (NGS) technologies has transformed genomic as well as transcriptomic analysis. NGS platforms offer massively parallel sequencing that can rapidly and comprehensively cover the human genome and detect low frequency genetic variants. Huge amounts of molecular data can be generated by whole-genome sequencing, whole-exome sequencing, RNA-seq, as well as targeted sequencing. Multiplex PCR is another platform that can be used for targeted sequencing.

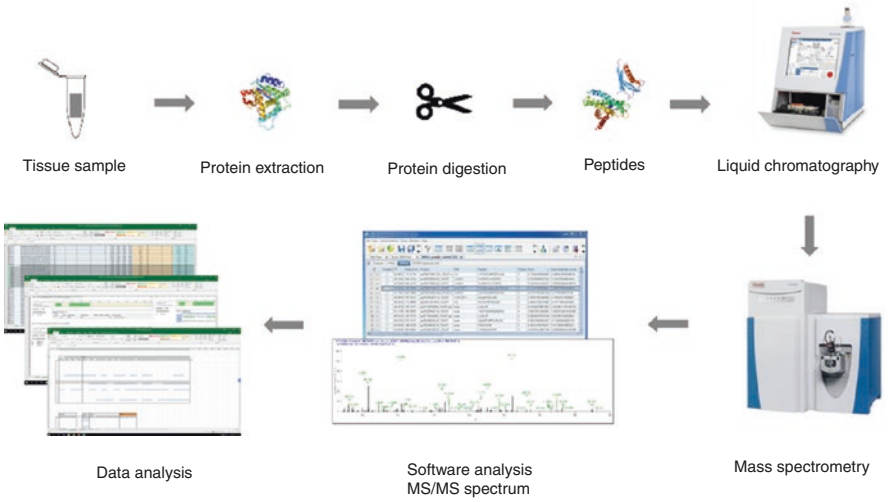

Fig. 31.3 Principles of mass spectrometry-based biomarker discovery

Mass spectrometry has been crucial for the development of proteomics and for high-throughput protein biomarker discovery (Fig. 31.3). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) combines the separating power of liquid chromatography with the mass analysis of triple quadrupole mass spectrometry. Targeted quantification of biomarker candidates using mass spectrometry can be performed with Selected/Multiple Reaction Monitoring (SRM/MRM) or Parallel Reaction Monitoring (PRM). Antibody-based proteomic methods are important complements to MS, especially for biofluids, where protein expression covers a wide dynamic range. Biofluid biomarkers can be measured by a variety of antibody-based technologies, such as enzyme-linked immunosorbent assay (ELISA), multiplex immunoassays and Reverse Phase Protein Arrays (RPPA).

Integration of omics data is a promising new approach, which is referred to as "proteogenomics" [22]. In this approach, customized sequence databases are generated that include genomic, transcriptomic and proteomic sequencing data (Fig. 31.4). The proteogenomics strategy can help understand which gene variants are translated to proteins, and thereby improve gene models, but also facilitate the discovery of new protein coding loci.

31.4 Diagnostic Biomarkers

Most patients with pancreatic cancer are identified once their disease has progressed to an advanced stage, contributing to the poor survival [23]. The ideal diagnostic biomarker for pancreatic cancer should be non-invasive, cost-effective and be able to detect early invasive cancers or high-risk lesions with a high degree of sensitivity

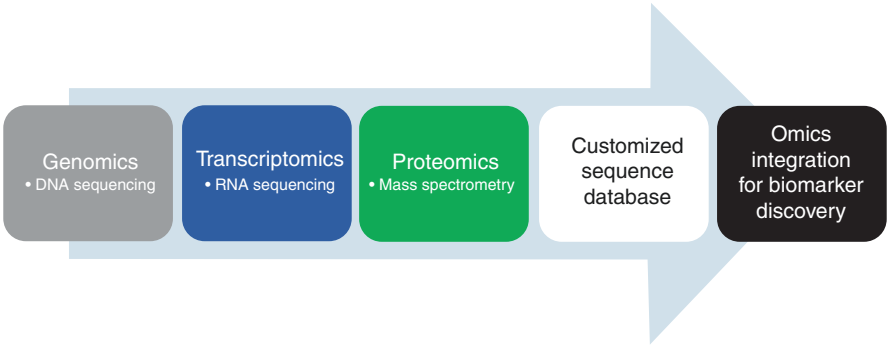

Fig. 31.4 An integrated omics approach for biomarker discovery

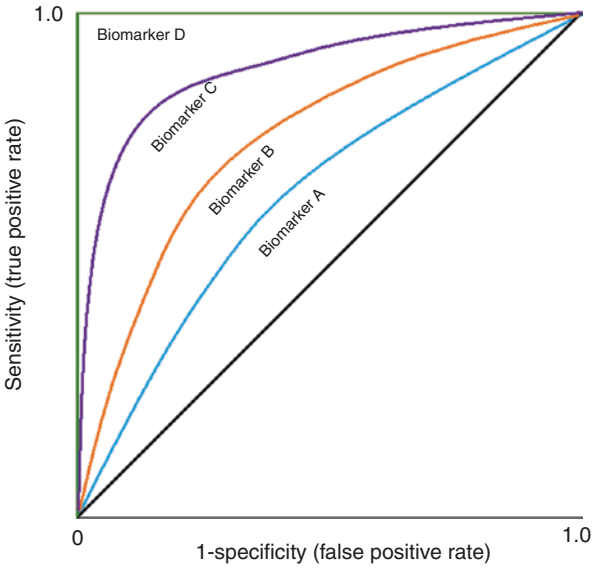

Fig. 31.5 Receiver operating characteristic (ROC) curve showing the diagnostic accuracy of four different biomarkers. The area under the curve (AUC) measures the area underneath each ROC curve and can be used to compare the different tests. The AUC ranges in value from 0 to 1. An AUC value of 1 indicates a perfect classifier. In this example, biomarker D has the highest diagnostic accuracy, followed by biomarker C, biomarker B and biomarker A

and specificity. The accuracy of the selected biomarkers, including sensitivity and specificity, depends on the cut-off levels that are chosen on a continuous scale. Receiver operating characteristic (ROC) curve analysis is a graphical approach for showing accuracy across the entire range of biomarker concentrations and the area under curve (AUC) provides an objective statistical method to assess the diagnostic accuracy, as shown in Fig. 31.5. ROC analysis avoids confounding resulting from subjective thresholds and is essential to modern biomarker research [24, 25].

The STARD-guidelines should be adhered to when reporting the diagnostic accuracy of candidate biomarkers (Table 31.1) [26].

It is important to distinguish between diagnostic tests and screening tests. A diagnostic test evaluates the presence/absence of disease in symptomatic individuals or provides a confirmatory test in people who screen positive for disease. On the other hand, a screening test aims to detect early disease or risk factors for disease in apparently healthy, asymptomatic individuals. Examples of screening tests include prostate-specific antigen (PSA), pap smear, fecal occult blood test, mammography and colonoscopy.

Table 31.2 summarizes a panel of novel blood-based biomarkers for pancreatic cancer. However, their diagnostic potentials are all derived from retrospective studies and they need to be validated in independent prospective studies.

Table 31.1 Guidelines for biomarker studies

Application	Guideline	Details	Ref
Biospecimen handling and processing	BRISQ	Recommendations for collecting, processing and storing human biospecimens.	[82]
Diagnostic biomarkers	STARD	Improving the reporting of diagnostic accuracy studies. 30-item checklist.	[26]
Prognostic biomarkers	REMARK	Recommendations for reporting biomarker prognostic studies. 20-item checklist.	[44]

Table 31.2 Blood-based diagnostic biomarkers in pancreatic cancer

Category	Example	Sensitivity	Specificity	AUC	Ref
Conventional biomarker	CA 19-9	80%	80%	0.87	[29]
Glycoproteins	THBS2 + CA 19-9	87%	98%	0.97	[31]
Cytokines	MIC-1	80%	85%	0.89	[34]
Stromal markers	MMP7 + CA19-9 (PC vs. HC)	Not stated	Not stated	0.99	[36]
	CCN2 + CA19-9 (PC vs. HC)	Not stated	Not stated	0.96	
	CCN2 + PLG + FN + Col4 + CA19-9 (PC vs. pancreatitis)	Not stated	Not stated	0.94	
Biomarker signatures	29 protein marker panel	95%	94%	0.96	[38]
ctDNA + protein markers	16 ctDNA mutations + 8 protein markers	70%	99.5%	0.91	[39]
Nucleosomes	5MC + H2AZ + H2A1.1 + H3K4Me2 + CA 19-9	92%	90%	0.98	[40]
microRNAs	2-microRNA panel	79%	85%	0.93	[41]
Exosomes	Glypican 1-positive exosomes	100%	100%	1.0	[43]

AUC area under the curve, *ctDNA* circulating tumor DNA, *HC* healthy controls, *PC* pancreatic cancer

31.4.1 CA 19-9

CA 19-9 is a sialylated Lewis A blood group antigen that is expressed on circulating mucins. It was originally isolated from a colorectal cancer cell line in 1979 [27], and in 1981 CA 19-9 was also found to be expressed in serum from pancreatic cancer patients [28]. The sensitivity/specificity of CA 19-9 is 80%/80% with an area under the curve (AUC) of 0.87 [29]. Levels of CA 19-9 can be elevated in several non-tumoral conditions, such as benign biliary obstruction or pancreatitis. Furthermore, Lewis-negative patients (about 5–7% of the population) cannot produce CA 19-9 levels, leading to false negative results. Despite these limitations, CA 19-9 is still the benchmark by which to compare and evaluate new candidate biomarkers [30].

31.4.2 THBS2

THBS2 is a glycoprotein that may function as an angiogenesis inhibitor. THBS2 was identified amongst secreted proteins released from human precursor PanIN organoids [31, 32]. In a series of human plasma validation studies, THBS2 discriminated between pancreatic cancer and controls with AUCs ranging from 0.76 to 0.87. The combination of THBS2 and CA19-9 provided a sensitivity of 87% at 98% specificity, with an AUC 0.97 [31].

31.4.3 MIC-1

Macrophage inhibitory cytokine-1 (MIC-1) belongs to the transforming growth factor beta (TGF-beta) superfamily. MIC-1 was found to be upregulated in pancreatic cancer tissues and elevated in the serum of pancreatic cancer patients compared with both healthy controls and those with benign pancreatic disease [33]. A subsequent meta-analysis reported that MIC-1 had a sensitivity of 80%, specificity of 85% and an AUC of 0.895 for diagnosing pancreatic cancer, which is comparable to CA 19-9 [34].

31.4.4 Stromal Markers

Pancreatic cancer is characterized by a dense stromal reaction with excessive extracellular matrix deposition. Stromal modifications appear to occur early in tumorigenesis [35], and circulating stromal markers may therefore provide a foundation for development of novel types of diagnosis. The plasma levels of stroma-associated biomarkers were found to distinguish pancreatic cancer from healthy controls with

high accuracy when used together with CA 19-9, including MMP7 and CA19-9 (AUC 0.99) and CCN2 and CA19-9 (AUC 0.96), while pancreatic cancer could be discriminated from chronic pancreatitis using a panel comprising CCN2, PLG, FN, Col4 and CA19-9 (AUC 0.94) [36].

31.4.5 Biomarker Signatures

Much data support the concept that a combination of biomarkers provide more diagnostic information than a single marker [37]. A biomarker signature comprising 29 biomarkers was found to provide high diagnostic accuracy (AUC 0.96) for diagnosing pancreatic cancer against healthy controls in a large retrospective study [38]. The AUC for discrimination between pancreatic cancer stages I-II and chronic pancreatitis was 0.84. The biomarker signature is currently being evaluated in a prospective study to detect pancreatic cancer in high-risk individuals (NCT03693378).

31.4.6 Combination of Circulating Tumor DNA and Protein Biomarkers

A proteogenomic blood test developed at Johns Hopkins University is designed to detect multiple cancer types at earlier stages of the disease [39]. The test, which is called CancerSEEK, measures circulating tumor DNA (ctDNA) from 16 genes, as well as eight proteins, and has been evaluated in patients with non-metastatic solid tumors including pancreatic cancer. The specificity is excellent (above 99%), but the sensitivity varies depending on tumor location, from 33% in breast cancer to 98% in ovarian cancer. The sensitivity for detecting pancreatic cancer was reported at 70%. The data are derived from a case-control study, but further prospective evaluation is necessary in general population cohorts where the test might be introduced.

31.4.7 Circulating Nucleosomes

Epigenetic changes include modifications to DNA that can affect gene expression, but do not change the DNA sequence. Sera from patients with pancreatic cancer have been found to contain distinct epigenetic alterations in DNA and histone proteins as part of circulating cell-free nucleosomes [40]. Combining CA 19-9 with a panel of four nucleosome biomarkers provides an AUC of 0.98 with an overall sensitivity of 92% at 90% specificity.

31.4.8 microRNAs

microRNAs (miRNAs) represent small, non-coding RNAs that are involved in the post-transcriptional regulation of protein expression. Some 32 blood-based miRNAs have been found to be upregulated in pancreatic cancer, while five miRNAs are reported to be downregulated [41]. Panels with different combinations of miRNAs provide AUCs in the range of 0.89–0.93.

31.4.9 Exosomes

Exosomes are nano-sized vesicles that mediate intercellular signaling. Exosomes have been implicated in cancer metastasis and treatment resistance in several tumor types [42]. Glypican 1 is a heparan sulphate proteoglycan that is bound to the cell surface membrane. In a seminal publication, circulating glypican 1-positive exosomes were reported to discriminate pancreatic cancer against healthy and benign controls with absolute precision [43]. The reported sensitivity was an impressive 100%, with a specificity of 100% and an AUC of 1.0.

31.5 Prognostic Biomarkers

Prognostic biomarkers indicate the likelihood of a future clinical event, such as disease progression, regardless of the treatment (Table 31.3). The REMARK guidelines should be followed when conducting prognostic biomarker studies (Table 31.1) [44]. However, the compliance to the REMARK guidelines in pancreatic cancer research has been limited [45].

31.5.1 CA 19-9

Pre-operative CA 19-9 serum levels provide useful prognostic information in patients with resectable tumors. CA 19-9 levels >37 U/mL have been found to be an independent prognostic factor of adverse outcome [46]. In non-operable pancreatic cancer, baseline CA19-9 levels >958 U/mL were found to be associated with poor survival [47].

Table 31.3 Prognostic biomarkers in pancreatic cancer

Biomarkers	HR (95% CI)	P-value	Ref
Blood			
CA 19-9 >37 U/mL (preoperative)	1.26 (1.20–1.32)	<0.001	[46]
CA 19-9 >948 U/mL (unresectable)	1.84 (1.31–2.57)	<0.001	[47]
CTCs	2.03 (1.14–3.63)	0.02	[58]
Tissue			
VEGF	1.51 (1.18–1.92)	0.001	[48]
SMAD4 loss	1.88 (1.31–2.70)	0.001	[52]
SPARC	1.53 (1.05–2.24)	0.03	[53]
S100A2	1.64 (1.33–2.02)	<0.001	[55]
S100A4	2.06 (1.30–3.28), at 12 months	<0.001	[55]
PD-L1	1.63 (1.34–1.98)	<0.001	[56]
miR-21	2.48 (1.96–3.14)	<0.001	[57]
Molecular subtypes	• Poor survival for quasi-mesenchymal subtype		[11]
	• Poor survival for basal-like subtype and classical subtype with activated stroma		[13]
	• Poor survival for squamous subtype		[9]

CI confidence interval, *CTCs* circulating tumor cells, *HR* hazard ratio

31.5.2 VEGF

Tumors promote angiogenesis by secreting pro-angiogenic factors, such as vascular endothelial growth factor (VEGF). VEGF is considered as one of the most important prognostic factors in resected pancreatic cancer [48, 49]. However, despite the prognostic role of VEGF, the success of anti-VEGF therapy in pancreatic cancer has been limited. The stromal compartment is believed to contribute to the low efficacy of anti-angiogenic agents in pancreatic cancer [50].

31.5.3 SMAD4

The SMAD4 gene encodes a transcription factor that is a crucial mediator of the TGF-beta signaling pathway. Inactivating mutations in SMAD4 occur in approximately half of pancreatic tumors [51]. Loss of SMAD4 expression has been found to be significantly correlated with poor overall survival [52].

31.5.4 SPARC

Secreted protein acidic and rich in cysteine (SPARC) is a matricellular glycoprotein with diverse functions, including involvement in tumor-stroma interactions. SPARC expression in the stroma has been found to be an independent prognostic factor of adverse survival in pancreatic cancer [53, 54].

31.5.5 S100 Proteins

S100 proteins are low molecular weight proteins with two calcium-binding EF-hand motifs. These proteins have regulatory roles in various cellular processes. Both S100A2 and S100A4 have been independently associated with poor survival in pancreatic cancer, and a preoperative nomogram incorporating S100A2 and S100A4 has been suggested to guide patient selection for surgery and neoadjuvant therapy [55].

31.5.6 PD-L1

Programmed cell death ligand-1 (PD-L1) is a central target for immunotherapy. PDL-1 is an immune checkpoint molecule that through binding to its ligand, programmed death-1 (PD-1), can down-regulate T-cell responses. PD-L1 is overexpressed in several neoplasms, including pancreatic cancer and facilitates immune escape of tumor cells and confers a poor prognosis [56].

31.5.7 microRNAs

The independent prognostic utility has been reported for several miRNAs, with most studies evaluating miR-21 [57].

31.5.8 Circulating Tumor Cells

Most cancer deaths are related to metastasis and not the primary tumor. Circulating tumor cells (CTCs) are important components of the metastatic cascade. The presence of CTCs has been associated with worse prognosis for pancreatic cancer patients [58].

31.5.9 Molecular Subtypes

Pancreatic cancer is a molecularly heterogeneous disease. In recent years, genomic and transcriptomic subtypes of pancreatic cancer have been proposed that are associated with prognosis. Collisson et al. [11] defined the classical, quasi-mesenchymal and exocrine-like subtypes. The quasi-mesenchymal subtype was associated with the worst survival. Moffitt et al. [13] proposed tumor subtypes that included epithelial, basal-like and classical subtypes, as well as stromal subtypes that included activated and normal stromal subtypes. The basal-like subtype and the activated stroma subtype in the classical subtype were associated with poor outcome. Bailey et al. [9] proposed four subtypes of pancreatic cancer, including squamous, pancreatic progenitor, ADEX and immunogenic subtypes. The squamous subtype was associated with poor prognosis.

31.6 Predictive Biomarkers

Predictive biomarkers provide information on the likelihood of benefit for specific therapies (Table 31.4).

Table 31.4 Predictive biomarkers in pancreatic cancer

Therapy	Biomarkers	Ref
Gemcitabine	hENT1	[60–63]
FOLFIRINOX	TS (5-FU), CES2 (irinotecan), BRCA1/2 (oxaliplatin), PALB2 (oxaliplatin)	[8, 65–68]
Nab-paclitaxel	No established marker	
Erlotinib	No established marker	
PARP inhibitor	BRCA1/2	[17, 75]
Stromal-targeting treatment	Hyaluronic acid (PEGPH20)	[77]
Immunotherapy	PD-L1, MSI/dMMR	[5, 16, 79, 80]
Treatment based on molecular subtype	• Quasi-mesenchymal subtype (gemcitabine); classical subtype (erlotinib)	[11]
	• Basal-like subtype (adjuvant chemotherapy); stroma-targeted therapies should be subtype directed	[13]
	• Squamous and immunogenic subtypes may benefit from metabolic and cell cycle inhibitors and immunotherapy	[9]

31.6.1 Gemcitabine Markers

Gemcitabine has been the mainstay of chemotherapy for pancreatic cancer since the 1990s [59]. The predictive role of hENT1 in gemcitabine treatment was initially evaluated by immunostaining in a small study [60]. These findings were validated several larger studies, including tissue samples from the randomized ESPAC-3 trial [61–63].

31.6.2 FOLFIRINOX Markers

FOLFIRINOX (folinic acid, 5-FU, irinotecan and oxaliplatin) has been reported to prolong survival in metastatic pancreatic cancer as compared to gemcitabine monotherapy [64]. Predictive biomarkers for the individual FOLFIRINOX components have been identified and include TS (5-FU) [65], CES2 (irinotecan) [66, 67], BRCA1/2 (oxaliplatin) [8] and PALB2 (oxaliplatin) [8, 68].

31.6.3 Nab-paclitaxel Markers

Nab-paclitaxel is an albumin-bound nanoparticle formulation of paclitaxel that is approved for the treatment of metastatic pancreatic cancer [69]. SPARC was initially believed to be a predictive marker of nab-paclitaxel drug sensitivity [70], but this finding could not be confirmed [71]. Currently, there is no validated marker for determining response to nab-paclitaxel.

31.6.4 Erlotinib

Erlotinib is an EGFR-specific tyrosine kinase inhibitor that has shown modest improvement in survival in metastatic pancreatic cancer [72]. However, EGFR gene copy number, mutations, polymorphisms and protein expression, or KRAS mutations have not shown predictive value in pancreatic cancer [73, 74].

31.6.5 Markers for PARP Inhibitors

PARP proteins are involved in a variety of DNA damage repair pathways, and PARP inhibitors disrupt their activity. The PARP inhibitor olaparib has shown promising antitumor activity in patients with metastatic pancreatic cancer and a

germline BRCA1/2 mutation [75]. Recently, the FDA approved olaparib for the maintenance treatment of patients with metastatic pancreatic cancer and a companion diagnostic test was approved for the identification of BRCA1/2 mutations [17].

31.6.6 Markers for Stromal-Targeting Treatment

Hyaluronic acid (HA) is a key component of the extracellular matrix. It is believed to raise interstitial fluid pressure in tumors and impede drug delivery [76]. PEGPH20 is a novel drug that may degrade HA to normalize interstitial fluid pressure and improve drug delivery. Initial data support tumor HA as a predictive biomarker for response [77]. A phase III trial is currently evaluating PEGPH20 together with nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic cancer and high HA (NCT02715804).

31.6.7 Immunotherapy Markers

Immunotherapy has had limited success in pancreatic cancer. Reasons include poor tumor immunogenicity and a highly immunosuppressive microenvironment [78]. The lack of reliable stratifying biomarkers is also a problem. However, promising predictive biomarkers are rapidly emerging. For immune checkpoint inhibitors, there are now several approved biomarkers, such as PD-L1 and MSI-high/dMMR, that can guide treatment decisions for various solid tumors [5, 16, 79, 80]. Pembrolizumab in MSI-high/dMMR tumors represents the first FDA approval for a biomarker-based therapy in pancreatic cancer, although the overall indication is organ-site agnostic [16]. MSI-high/dMMR is rare in pancreatic cancer (<1%), but is still important to identify given its potential to guide treatment decisions.

31.6.8 Directing Treatment by Molecular Subtype

Collisson et al. [11] suggested that the quasi-mesenchymal subtype is more sensitive to gemcitabine, while the classical subtype is more sensitive to erlotinib. Moffitt et al. [13] reported that the basal-like subtype benefits from adjuvant chemotherapy, while stroma-targeted therapies might need to be subtype directed. Bailey et al. [13] reported that squamous and immunogenic subtypes may benefit from metabolic and cell cycle inhibitors and immunotherapy. However, strong evidence of clinical utility is still lacking and the proposed molecular subtypes and their differing responses to treatment need to be validated in clinical trials.

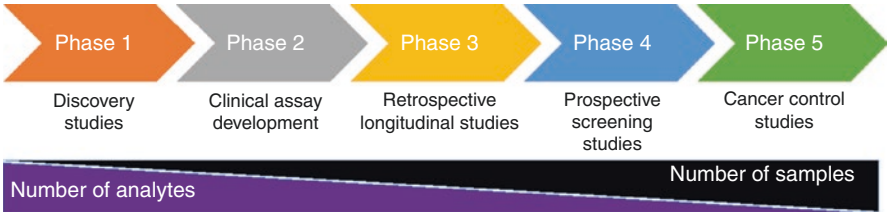

Fig. 31.6 Phases of biomarker development for early detection of pancreatic cancer. (Adapted from reference [81])

31.7 Phases of Biomarker Development

Translating investigational biomarkers to the clinic is a complex interdisciplinary issue. The demonstration of clinical utility is central, as well as cross-sector collaborations between patients, clinicians, researchers, funders, industry, regulators and policymakers. Pepe et al. [81] has suggested a structured 5-step model for biomarker translation (Fig. 31.6). Usually sample sizes increase and the numbers of analytes decrease as the biomarker assay moves from discovery to validation phases. Power calculations need be performed during all phases. Regulatory concerns must be taken into account when designing prospective trials for clinical validation.

31.8 Study Design Considerations

31.8.1 Sample Integrity

Sample quality has an essential role in omics research. It is possible to introduce confounding factors during sample collection due to poor handling. Consequently, all sample acquisition and biobank processes, including clinical documentation, need to be standardized. The Biospecimen Reporting for Improved Study Quality (BRISQ) [82] recommendations have been outlined for research involving human biospecimens (Table 31.1).

31.8.2 Data Analysis Including Machine Learning

The analysis of large amounts of multi-omics data can be quite challenging. In traditional research, the number of individuals in the study population (n) usually exceeds the number of examined variables (p). However, in translational biomarker

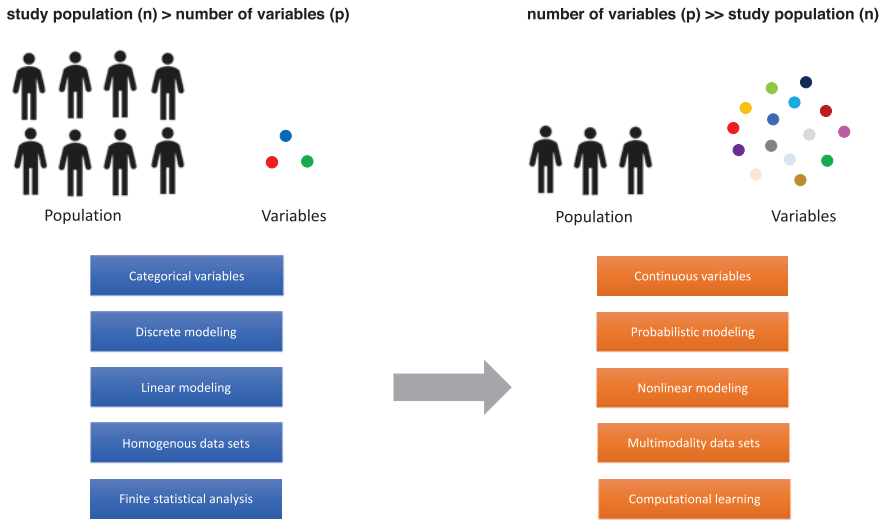

Fig. 31.7 Mathematical modeling of molecular data when the number of variables being investigated (p) exceeds the number of samples that make up the study population (n). (Adapted from reference [83])

studies it is common for $p \gg n$ [83]. Several strategies have been proposed to improve data modeling in these cases (Fig. 31.7). Machine learning algorithms, such as artificial neural networks, are well suited for multi-dimensional biomarker datasets [84]. There is a risk of overfitting the data when the model fits itself to the training data but is no longer able to make predictions in new patients. To overcome overfitting, cross-validation procedures and validations with independent data sets can be performed.

31.9 Conclusion

Many promising biomarkers have emerged in pancreatic cancer with potential clinical utility. By integrating different classes of omics data (genomics, transcriptomics, proteomics) a more holistic molecular perspective can be achieved, leading to a better characterization of disease genotypes and phenotypes. The CancerSEEK test is a good example of the high tumor specificity achieved through the integration of different omics approaches. In the era of "big" omics data, it is envisaged that machine learning techniques will play a critical role in finding predictive molecular patterns for complex diseases such as pancreatic cancer.

References

1. Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. N Engl J Med. 2017;377(9):849–61.
2. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16.
3. Duffy MJ, Harbeck N, Nap M, Molina R, Nicolini A, Senkus E, et al. Clinical use of biomarkers in breast cancer: updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017;75:284–98.
4. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016;17(12):e542–e51.
5. Luchini C, Bibeau F, Ligtenberg MJL, Singh N, Nottegar A, Bosse T, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol. 2019;30:1232–43.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
7. Duffy MJ, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441–7.
8. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
9. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531(7592):47–52.
10. Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012;491(7424):399–405.
11. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med. 2011;17(4):500–3.
12. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
13. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47(10):1168–78.
14. Bailey AM, Mao Y, Zeng J, Holla V, Johnson A, Brusco L, et al. Implementation of biomarker-driven cancer therapy: existing tools and remaining gaps. Discov Med. 2014;17(92):101–14.
15. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019;20(1):572.
16. FDA approves first cancer treatment for any solid tumor with a specific genetic feature. Accessed 13 Jan 2020. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature.
17. FDA approves olaparib for gBRCAm metastatic pancreatic adenocarcinoma. Accessed 13 Jan 2020. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-gbrcam-metastatic-pancreatic-adenocarcinoma.
18. Peabody JW, Shimkhada R, Tong KB, Zubiller MB. New thinking on clinical utility: hard lessons for molecular diagnostics. Am J Manag Care. 2014;20(9):750–6.
19. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89–95.
20. Chakraborty J, Midya A, Gazit L, Attiyeh M, Langdon-Embry L, Allen PJ, et al. CT radiomics to predict high-risk intraductal papillary mucinous neoplasms of the pancreas. Med Phys. 2018;45(11):5019–29.
21. Khalvati F, Zhang Y, Baig S, Lobo-Mueller EM, Karanicolas P, Gallinger S, et al. Prognostic value of CT radiomic features in resectable pancreatic ductal adenocarcinoma. Sci Rep. 2019;9(1):5449.

22. Zhang B, Whiteaker JR, Hoofnagle AN, Baird GS, Rodland KD, Paulovich AG. Clinical potential of mass spectrometry-based proteogenomics. Nat Rev Clin Oncol. 2019;16(4):256–68.
23. Ansari D, Bauden M, Bergstrom S, Rylance R, Marko-Varga G, Andersson R. Relationship between tumour size and outcome in pancreatic ductal adenocarcinoma. Br J Surg. 2017;104(5):600–7.
24. Soreide K. Receiver-operating characteristic curve analysis in diagnostic, prognostic and predictive biomarker research. J Clin Pathol. 2009;62(1):1–5.
25. Soreide K, Korner H, Soreide JA. Diagnostic accuracy and receiver-operating characteristics curve analysis in surgical research and decision making. Ann Surg. 2011;253(1):27–34.
26. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6(11):e012799.
27. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. Som Cell Genet. 1979;5(6):957–71.
28. Koprowski H, Herlyn M, Steplewski Z, Sears HF. Specific antigen in serum of patients with colon carcinoma. Science. 1981;212(4490):53–5.
29. Huang Z, Liu F. Diagnostic value of serum carbohydrate antigen 19-9 in pancreatic cancer: a meta-analysis. Tumour Biol. 2014;35(8):7459–65.
30. Haab BB, Huang Y, Balasenthil S, Partyka K, Tang H, Anderson M, et al. Definitive characterization of CA 19-9 in resectable pancreatic cancer using a reference set of serum and plasma specimens. PLoS One. 2015;10(10):e0139049.
31. Kim J, Bamlet WR, Oberg AL, Chaffee KG, Donahue G, Cao XJ, et al. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. Sci Transl Med. 2017;9(398):eaah5583.
32. Kim J, Hoffman JP, Alpaugh RK, Rhim AD, Reichert M, Stanger BZ, et al. An iPSC line from human pancreatic ductal adenocarcinoma undergoes early to invasive stages of pancreatic cancer progression. Cell Rep. 2013;3(6):2088–99.
33. Koopmann J, Buckhaults P, Brown DA, Zahurak ML, Sato N, Fukushima N, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res. 2004;10(7):2386–92.
34. Yang Y, Yan S, Tian H, Bao Y. Macrophage inhibitory cytokine-1 versus carbohydrate antigen 19-9 as a biomarker for diagnosis of pancreatic cancer: a PRISMA-compliant meta-analysis of diagnostic accuracy studies. Medicine (Baltimore). 2018;97(9):e9994.
35. Korc M. Pancreatic cancer-associated stroma production. Am J Surg. 2007;194(4 Suppl):S84–6.
36. Resovi A, Bani MR, Porcu L, Anastasia A, Minoli L, Allavena P, et al. Soluble stroma-related biomarkers of pancreatic cancer. EMBO Mol Med. 2018;10(8):e8741.
37. Chatterjee SK, Zetter BR. Cancer biomarkers: knowing the present and predicting the future. Future Oncol. 2005;1(1):37–50.
38. Mellby LD, Nyberg AP, Johansen JS, Wingren C, Nordestgaard BG, Bojesen SE, et al. Serum biomarker signature-based liquid biopsy for diagnosis of early-stage pancreatic cancer. J Clin Oncol. 2018;36(28):2887–94.
39. Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018;359(6378):926–30.
40. Bauden M, Pamart D, Ansari D, Herzog M, Eccleston M, Micallef J, et al. Circulating nucleosomes as epigenetic biomarkers in pancreatic cancer. Clin Epigenetics. 2015;7:106.
41. Wei L, Yao K, Gan S, Suo Z. Clinical utilization of serum- or plasma-based miRNAs as early detection biomarkers for pancreatic cancer: a meta-analysis up to now. Medicine (Baltimore). 2018;97(35):e12132.
42. Ruivo CF, Adem B, Silva M, Melo SA. The biology of cancer exosomes: insights and new perspectives. Cancer Res. 2017;77(23):6480–8.
43. Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature. 2015;523(7559):177–82.
44. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM, et al. REporting recommendations for tumour MARKer prognostic studies (REMARK). Br J Cancer. 2005;93(4):387–91.

45. Petrushnko W, Gundara JS, De Reuver PR, O'Grady G, Samra JS, Mittal A. Systematic review of peri-operative prognostic biomarkers in pancreatic ductal adenocarcinoma. HPB (Oxford). 2016;18(8):652–63.
46. Bergquist JR, Puig CA, Shubert CR, Groeschl RT, Habermann EB, Kendrick ML, et al. Carbohydrate antigen 19-9 elevation in anatomically resectable, early stage pancreatic cancer is independently associated with decreased overall survival and an indication for neoadjuvant therapy: a national cancer database study. J Am Coll Surg. 2016;223(1):52–65.
47. Maisey NR, Norman AR, Hill A, Massey A, Oates J, Cunningham D. CA19-9 as a prognostic factor in inoperable pancreatic cancer: the implication for clinical trials. Br J Cancer. 2005;93(7):740–3.
48. Smith RA, Tang J, Tudur-Smith C, Neoptolemos JP, Ghaneh P. Meta-analysis of immunohistochemical prognostic markers in resected pancreatic cancer. Br J Cancer. 2011;104(9):1440–51.
49. Ansari D, Rosendahl A, Elebro J, Andersson R. Systematic review of immunohistochemical biomarkers to identify prognostic subgroups of patients with pancreatic cancer. Br J Surg. 2011;98(8):1041–55.
50. Craven KE, Gore J, Korc M. Overview of pre-clinical and clinical studies targeting angiogenesis in pancreatic ductal adenocarcinoma. Cancer Lett. 2016;381(1):201–10.
51. Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science. 1996;271(5247):350–3.
52. Shugang X, Hongfa Y, Jianpeng L, Xu Z, Jingqi F, Xiangxiang L, et al. Prognostic value of SMAD4 in pancreatic cancer: a meta-analysis. Transl Oncol. 2016;9(1):1–7.
53. Han W, Cao F, Chen MB, Lu RZ, Wang HB, Yu M, et al. Prognostic value of SPARC in patients with pancreatic cancer: a systematic review and meta-analysis. PLoS One. 2016;11(1):e0145803.
54. Gundewar C, Sasor A, Hilmersson KS, Andersson R, Ansari D. The role of SPARC expression in pancreatic cancer progression and patient survival. Scand J Gastroenterol. 2015;50(9):1170–4.
55. Dreyer SB, Pinese M, Jamieson NB, Scarlett CJ, Colvin EK, Pajic M, et al. Precision oncology in surgery: patient selection for operable pancreatic cancer. Ann Surg. 2018;
56. Hu Y, Chen W, Yan Z, Ma J, Zhu F, Huo J. Prognostic value of PD-L1 expression in patients with pancreatic cancer: a PRISMA-compliant meta-analysis. Medicine (Baltimore). 2019;98(3):e14006.
57. Frampton AE, Krell J, Jamieson NB, Gall TM, Giovannetti E, Funel N, et al. microRNAs with prognostic significance in pancreatic ductal adenocarcinoma: a meta-analysis. Eur J Cancer. 2015;51(11):1389–404.
58. Stephenson D, Nahm C, Chua T, Gill A, Mittal A, de Reuver P, et al. Circulating and disseminated tumor cells in pancreatic cancer and their role in patient prognosis: a systematic review and meta-analysis. Oncotarget. 2017;8(63):107223–36.
59. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
60. Spratlin J, Sangha R, Glubrecht D, Dabbagh L, Young JD, Dumontet C, et al. The absence of human equilibrative nucleoside transporter 1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma. Clin Cancer Res. 2004;10(20):6956–61.
61. Bird NT, Elmasry M, Jones R, Psarelli E, Dodd J, Malik H, et al. Immunohistochemical hENT1 expression as a prognostic biomarker in patients with resected pancreatic ductal adenocarcinoma undergoing adjuvant gemcitabine-based chemotherapy. Br J Surg. 2017;104(4):328–36.
62. Farrell JJ, Elsaleh H, Garcia M, Lai R, Ammar A, Regine WF, et al. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. Gastroenterology. 2009;136(1):187–95.
63. Greenhalf W, Ghaneh P, Neoptolemos JP, Palmer DH, Cox TF, Lamb RF, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst. 2014;106(1):djt347.
64. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.

65. Hu YC, Komorowski RA, Graewin S, Hostetter G, Kallioniemi OP, Pitt HA, et al. Thymidylate synthase expression predicts the response to 5-fluorouracil-based adjuvant therapy in pancreatic cancer. Clin Cancer Res. 2003;9(11):4165–71.
66. Capello M, Lee M, Wang H, Babel I, Katz MH, Fleming JB, et al. Carboxylesterase 2 as a determinant of response to irinotecan and neoadjuvant FOLFIRINOX therapy in pancreatic ductal adenocarcinoma. J Natl Cancer Inst. 2015;107(8):djv132.
67. Khanna R, Morton CL, Danks MK, Potter PM. Proficient metabolism of irinotecan by a human intestinal carboxylesterase. Cancer Res. 2000;60(17):4725–8.
68. Villarroel MC, Rajeshkumar NV, Garrido-Laguna I, De Jesus-Acosta A, Jones S, Maitra A, et al. Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer. Mol Cancer Ther. 2011;10(1):3–8.
69. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
70. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol. 2011;29(34):4548–54.
71. Hidalgo M, Plaza C, Musteanu M, Illei P, Brachmann CB, Heise C, et al. SPARC expression did not predict efficacy of nab-paclitaxel plus gemcitabine or gemcitabine alone for metastatic pancreatic cancer in an exploratory analysis of the phase III MPACT trial. Clin Cancer Res. 2015;21(21):4811–8.
72. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
73. Boeck S, Jung A, Laubender RP, Neumann J, Egg R, Goritschan C, et al. KRAS mutation status is not predictive for objective response to anti-EGFR treatment with erlotinib in patients with advanced pancreatic cancer. J Gastroenterol. 2013;48(4):544–8.
74. Propper D, Davidenko I, Bridgewater J, Kupcinskas L, Fittipaldo A, Hillenbach C, et al. Phase II, randomized, biomarker identification trial (MARK) for erlotinib in patients with advanced pancreatic carcinoma. Ann Oncol. 2014;25(7):1384–90.
75. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–27.
76. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(3):418–29.
77. Hingorani SR, Zheng L, Bullock AJ, Seery TE, Harris WP, Sigal DS, et al. HALO 202: randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J Clin Oncol. 2018;36(4):359–66.
78. Andersson R, Pereira C, Bauden M, Ansari D. Is immunotherapy as a holy grail in pancreatic cancer. Immunotherapy. 2019;11:1435.
79. Arora S, Velichinskii R, Lesh RW, Ali U, Kubiak M, Bansal P, et al. Existing and emerging biomarkers for immune checkpoint immunotherapy in solid tumors. Adv Ther. 2019;36:2638.
80. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–13.
81. Pepe MS, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, et al. Phases of biomarker development for early detection of cancer. J Natl Cancer Inst. 2001;93(14):1054–61.
82. Moore HM, Kelly AB, Jewell SD, McShane LM, Clark DP, Greenspan R, et al. Biospecimen reporting for improved study quality (BRISQ). Cancer Cytopathol. 2011;119(2):92–101.
83. Marko NF, Weil RJ. Mathematical modeling of molecular data in translational medicine: theoretical considerations. Sci Transl Med. 2010;2(56):56rv4.
84. Camacho DM, Collins KM, Powers RK, Costello JC, Collins JJ. Next-generation machine learning for biological networks. Cell. 2018;173(7):1581–92.

Chapter 32
Difficult Diagnosis and Differentials to a Solid Pancreatic Tumour

Ville J. Sallinen and Helka Parviainen

Take Home Messages

- Computed tomography is the gold standard first line imaging study for pancreatic tumors, and magnetic resonance imaging second line imaging of choice
- Brush cytology is the diagnostic method of choice in patients requiring biliary stenting
- Endoscopic ultrasound guided sampling is the cornerstone in many equivocal tumours
- The differential diagnoses for a pancreatic tumour can be divided into four entities: (1) malignant neoplasia, (2) benign neoplasia, (3) inflammatory lesions, (4) normal anatomy or anomaly
- IgG4 and CA19-9 are the most important biomarkers in differential diagnosis of a solid pancreatic tumour.

Pearls and Pitfalls

- Different types of pancreatitis (autoimmune, chronic, focal) pose the greatest difficulty in the differential diagnostics of a pancreatic tumour
- Surgery is recommended for a pancreatic tumour even in the absence of unequivocal findings after extensive diagnostic work-up if suspicion for malignancy remains, but needs to be carefully discussed with the patient.
- Rare differential diagnoses, such as tuberculosis and lymphoma, must be kept in mind as these might be medically curable.

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Future Perspectives

- Diagnostic methods to evaluate pancreatic tumor are still far from perfect and new modalities need to be developed. Although both the continuous improvement of the conventional imaging methods and the development of new methods such as endoscopic ultrasound elastography and new molecular imaging targets will lead to improved accuracy, it is likely that major breakthroughs will occur in the field of serum biomarkers in the future.

32.1 Introduction

When diagnosis is clear, tumour resectable and patient fit, proceeding to resection for pancreatic cancer is relatively straightforward. Solid pancreatic tumours are an entity where pretreatment diagnosis may sometimes be extremely difficult if not impossible to obtain. Imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) may be misleading and signs of malignancy absent. Accuracy of brush cytology obtained via endoscopic retrograde cholangiography (ERC) is around 40–70% only and might thus suggest benign origin despite malignancy [1]. Needle biopsy can be difficult or impossible to obtain due to proximity of large vessels or fear of tumour seeding. Endoscopic ultrasound alleviates some of the problems associated with percutaneous sampling, but it is extremely dependent on the operator. Possibility of false negative result and biopsy related complications must also be taken into account. Further, numerous benign conditions may mimic pancreatic cancer making decision to proceed to notoriously complication-prone surgery even more difficult. On the other hand, laborious preoperative work-up and diagnostic procedures will inevitably take time, predisposing the patient to local tumour progression or dissemination. Modern imaging technology has made diagnosis without histology more certain. But still sometimes pancreatic surgeon finds her/himself in a position where one needs to discuss with the patient the potential risks of wait-and-see versus prompt surgery for a diagnosis that is not entirely certain. The rate of benign disease in patients undergoing pancreatoduodenectomy for a suspected malignancy has been reported to be around 10% (most usually pancreatitis) [1].

32.2 Diagnostic Work-Up

Outline of diagnostic work-up of a pancreatic tumour is presented in Fig. 32.1. Computed tomography is the gold standard first line imaging option in patients with suspected pancreatic tumour and is sufficient in the vast majority of patients. Patients with pancreatic head tumor associated with biliary obstruction are recommended to be operated without preoperative biliary stenting if possible. However, if

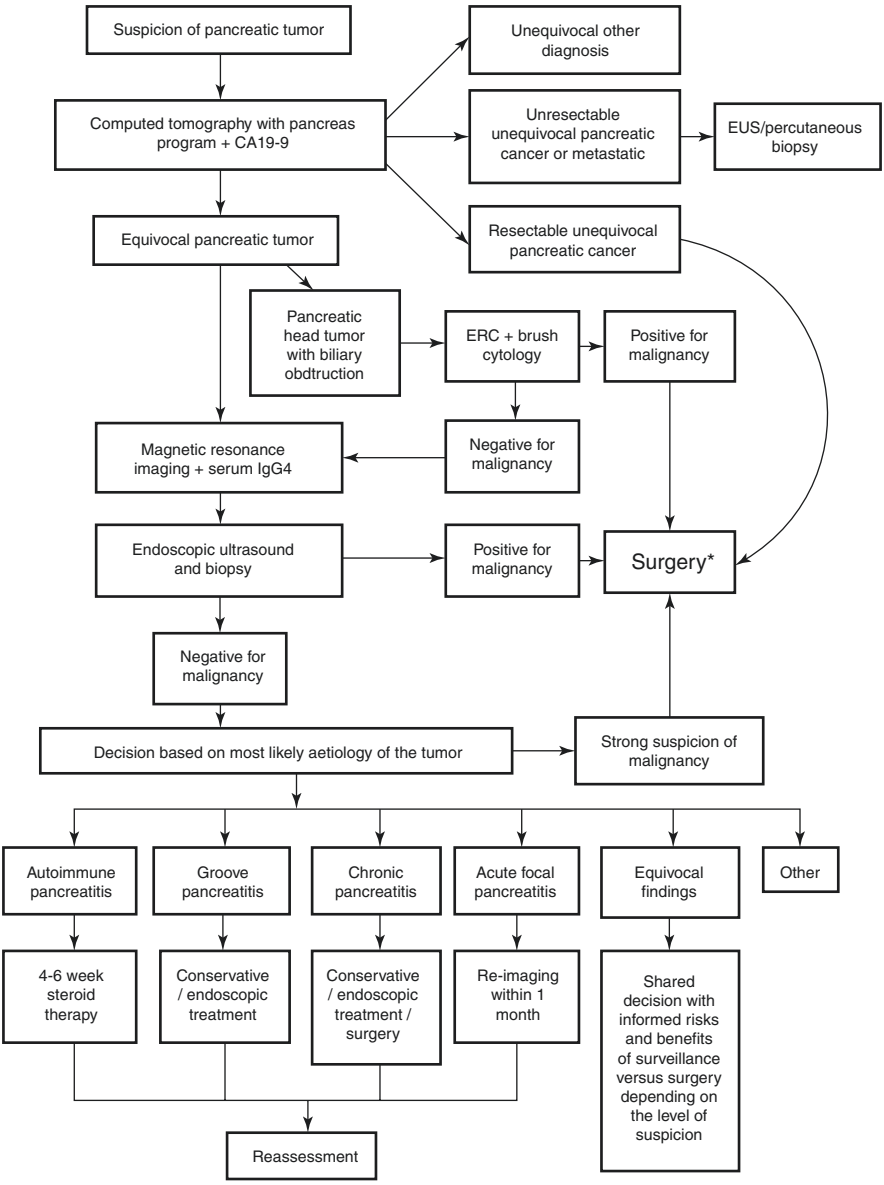

Fig. 32.1 Outline of diagnostic work-up of a pancreatic tumour. *Surgery refers to appropriate surgical resection with or without neoadjuvant therapy in patients fit for surgery with resectable or borderline resectable tumors, and is covered in more detail in other chapters of this book

the diagnosis is equivocal and biliary obstruction is present, ERCP with brush cytology sampling is the method of choice to obtain proof of malignancy. MRI is the second line imaging option in patients with equivocal findings in CT and/or ERCP. Serum markers CA19-9 and IgG4 may give hints on the etiology of the lesion, and are discussed in more detail later in this chapter. If the diagnosis is

equivocal despite aforementioned work-up, endoscopic ultrasound is the method of choice and has become the cornerstone in the diagnostics of these lesions.

32.3 Differential Diagnoses of a Pancreatic Tumour

Following sections will discuss differential diagnoses in solid pancreatic tumours and how to approach them diagnostically. Discussion of cystic pancreatic tumours is found in other chapters in this book. Table 32.1 summarizes the differential diagnoses of a pancreatic tumour.

Table 32.1 Pancreatic ductal adenocarcinoma and its mimickers: typical diagnostic findings

	History and clinical findings[a]	Serology[b]	Cross-sectional imaging
Ductal adenocarcinoma	weight loss, upper abdominal pain	Ca-19-9 ↑	hypodense infiltrating mass, abrupt duct occlusion
Autoimmune pancreatitis	history of autoimmune disease	IgG4 ↑	enlarged "sausage" pancreas or focal hypodense enlargement; restricted diffusion in DWI; ± extrapancreatic manifestations
Groove pancreatitis	history of alcohol abuse and smoking, weight loss, upper abdominal pain		hypodense fibrous tissue in pancreatic groove, thickened medial duodenal wall ± cysts
Chronic pancreatitis	history of pancreatitis, weight loss, upper abdominal pain		atrophy, calcifications, irregular duct dilatation and strictures
Acute focal pancreatitis	upper abdominal pain	Amylase ↑ CRP ↑	Focal mass with cystic components, surrounding oedema, resolves in follow-up
Pancreatic lymphoma	young patients, upper abdominal pain	LD ↑ B2M ↑ IgG4 →	hypodense mass, restricted diffusion in DWI, incases vessels without obstruction
Metastases	history of extrapancreatic malignancy	Corresponding tumor markers ↑	mass with variable characteristics, may be multifocal, extrapancreatic metastases
Benign tumors	usually asymptomatic		mass with sharp borders
Mimickers of neoplasia	history of tuberculosis, sarcoidosis or other condition		mass with variable characteristics, may be multifocal; extrapancreatic manifestations

IgG4 immunoglobulin G4, *DWI* diffusion-weighted imaging, *CRP* C-reactive protein, *LD* lactate dehydrogenase, *B2M* beta-2 microglobulin

[a]Jaundice may be present in all entities, if bile duct is obstructed by the condition

[b]Ca-19-9 may be elevated in all entities due to bile duct obstruction

32.4 Autoimmune Pancreatitis

Two types of autoimmune pancreatitis are distinguished. Type 1 autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis) is more often present in elderly patients, especially in males, and it is associated usually with elevated serum IgG4 and histologically IgG4 positive plasma cells. Type 1 autoimmune pancreatitis may present with extrapancreatic organ manifestation which include orbital pseudotumor, IgG4-associated cholangitis, exocrinopathy of the salivary gland, tubulointerstitial nefritis, and pulmonary, mediastinal or retroperitoneal fibrosis [2]. Although extrapancreatic organ manifestation distinguishes autoimmune pancreatitis from pancreatic cancer, renal, retroperitoneal, and mediastinal involvement may also be present in pancreatic lymphoma [3]. Usual presentation of Type 1 autoimmune pancreatitis is a painless obstructive jaundice, similar to pancreatic cancer.

Patients with Type 2 autoimmune pancreatitis (Idiopathic duct-centric pancreatitis) are usually younger, aa often women as men, and present with recurrent pancreatitis, but Type 2 autoimmune pancreatitis might also manifest as a painless jaundice. It is associated with inflammatory bowel disease (particularly ulcerative colitis), but it does have extrapancreatic organ manifestations. Only every fourth patient has elevated serum IgG4 levels [4].

Two most commonly used criteria to diagnose autoimmune pancreatitis are HISORt (Histology, Imaging, Serology, Other organ, Response to therapy) criteria [5] and ICDC criteria (International Consensus Diagnostic Criteria) [6], which largely overlap one another.

Typical computed tomography (CT) imaging feature of both types of autoimmune pancreatitis is diffuse enlargement and delayed enhancement of the whole pancreas (sausage pancreas). However, similar diffuse or segmental enlargement may be seen in pancreatic lymphoma [3]. In one third of autoimmune pancreatitis patients a low-attenuating rim-like capsule is present. FDG-PET-CT scan may show increased signal in areas of inflammation and is usually not helpful in the initial diagnosis, but it may be used in follow-up to detect resolving inflammation following treatment with steroids. Magnetic resonance imaging (MRI) findings are similar to CT in terms of morphology and enhancement, but MRI has the added value of diffusion weighted imaging (DWI) which shows a typical diffusion restriction that resolves with treatment (Fig. 32.2). The restriction is generally more prominent in autoimmune pancreatitis than adenocarcinoma, but there may be significant overlap [7]. Radiologically differentiating autoimmune pancreatitis from adenocarcinoma is not difficult when the whole pancreas is affected, but a focal mass is seen in over half of the patients (Fig. 32.3).

Serum IgG4 is one of the cornerstones in autoimmune pancreatitis diagnostics. Using a threshold of IgG4 >2 times of the normal upper limit leads to lower sensitivity, but to very high specificity up to 99% [8]. Every tenth patient with a pancreatic cancer may have elevated IgG4 levels, but only 1% have >2 times the normal upper limit [8]. CA19-9 levels are lower in patients with autoimmune pancreatitis compared with pancreatic cancer, but CA19-9 levels alone are not accurate enough

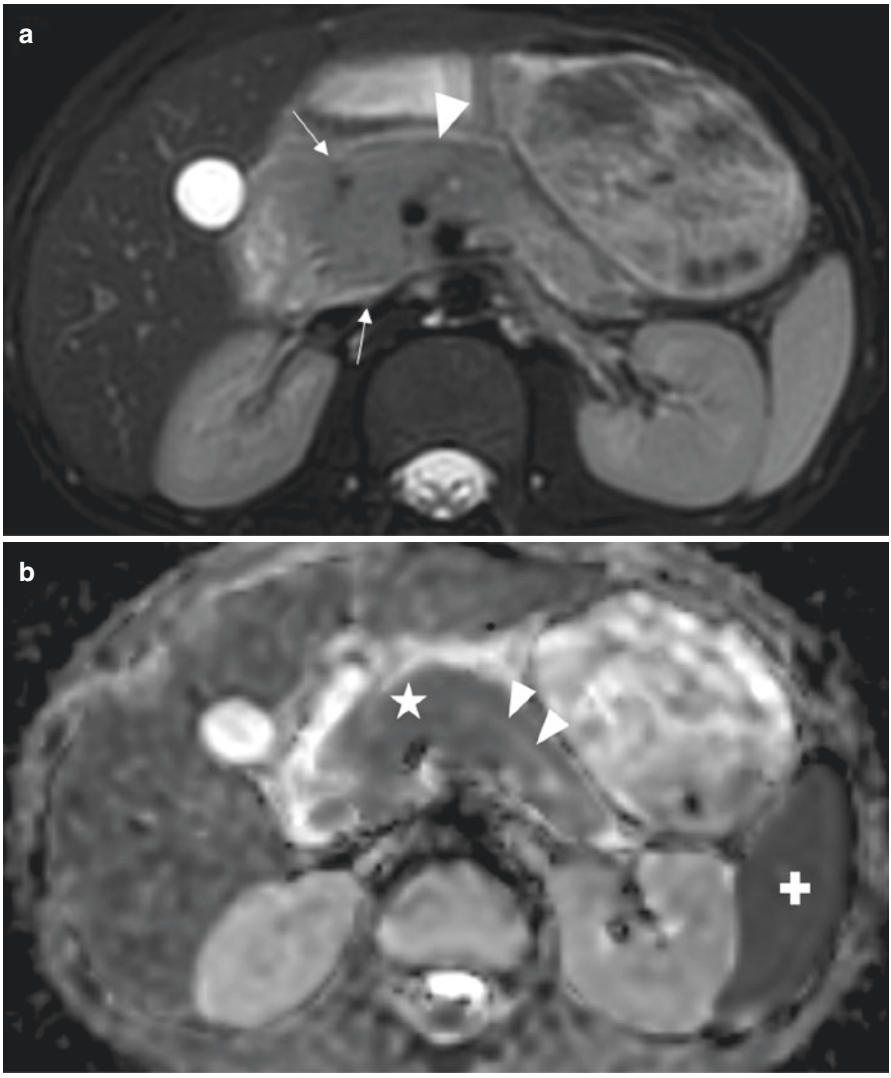

Fig. 32.2 Diffuse autoimmune pancreatitis. 10-year-old boy presented with upper abdominal pain. In T2-weighted fat saturated MRI (**a**), the whole pancreas is diffusely enlarged, especially the head (arrows), and surrounded by a very thin T2-hypointense capsule (arrowhead). In diffusion-weighted imaging (**b**), diffusion restriction in the pancreatic parenchyma is seen as dark signal in the ADC map (star). The spleen (+) has an even stronger diffusion restriction, which is a normal finding. The "duct penetrating sign" favoring a non-neoplastic mass is also demonstrated here (arrowheads). A large core needle biopsy was performed and the histological and immunohistochemical findings were consistent with IgG4-associating autoimmune pancreatitis

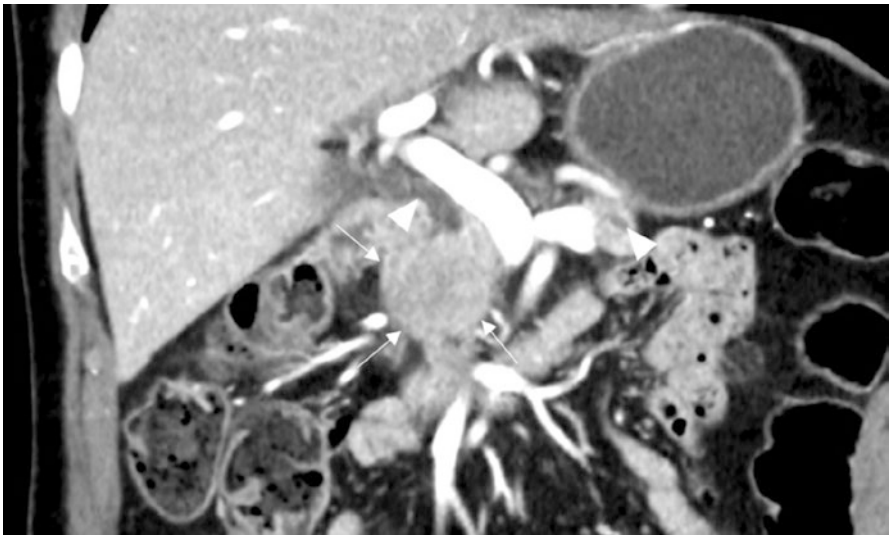

Fig. 32.3 Focal autoimmune pancreatitis. Patient in her 60s presented with abdominal pain and diarrhea. In CT, a large pancreatic head mass was seen (arrows). It caused a borderline bile duct and main pancreatic duct (arrowheads) dilatation. Ultrasound-guided percutaneous large core needle biopsy was performed, and the histology was consistent with pancreatitis with an IgG4-positive immunohistochemical stain. In a CT after 3 months of steroid treatment, pancreas was normal

for diagnosis. Combination of CA19-9 levels (below 85 U/ml) and elevated IgG4 provides good discrimination of autoimmune pancreatitis and pancreatic cancer with sensitivity and specificity around 90% [9, 10].

Unlike in chronic pancreatitis, in which pancreaticoduodenectomy is an acceptable treatment modality, all efforts to diagnose and distinguish autoimmune pancreatitis from chronic pancreatitis or pancreatic cancer should be made as simple steroid treatment could be enough to resolve the inflammation and prevent the unnecessary operation. Having said that, autoimmune pancreatitis is present in approximately every third patient who has undergone pancreaticoduodenectomy for presumed pancreatic cancer with ultimately benign histology [11, 12]. In cases where both pancreatic cancer and autoimmune pancreatitis are possible diagnostic alternatives, serum IgG4 levels and EUS-guided large core needle biopsy are recommended to obtain more certain diagnosis [1]. Further, if the biopsy is not diagnostic or suspicious for malignancy, a short course (4–6 weeks) steroid treatment is recommended to differentiate autoimmune pancreatitis from pancreatic cancer [1]. Keep in mind though that pancreatic lymphoma might also respond to steroid treatment initially [3].

32.5 Acute Focal Pancreatitis

Acute pancreatitis, especially its focal form, can be extremely difficult to discern from pancreatic cancer. Both may form an inflammatory mass, cause duct dilatation, and show encasement of vascular structures [13, 14]. The inflammation in acute pancreatitis may mask the underlying mass.

To make differential diagnosis even more difficult, pancreatic cancer may in fact cause acute pancreatitis, and pancreatitis and pancreatic cancer may co-exist. Only 1–2% of pancreatitis are caused by pancreatic cancer and 3% of pancreatic cancers present as pancreatitis [13]. Five percent of pancreatitis, in which no etiological factor is found, turn out to be caused by pancreatic cancer [13]. Suspicion of pancreatic cancer should be raised especially in cases of older patients without risk factors for pancreatitis (bile stones, alcohol abuse, pancreas divisum) as well as in cases with signs of both pancreatic duct and bile duct dilatation (double duct sign) and abrupt obstruction of pancreatic duct.

Biopsy is not recommended during the acute inflammatory period. Follow-up imaging is the best option in unclear cases and should be performed within a month [14], preferably by using both MRI and CT. To support the diagnosis of focal pancreatitis, the mass-like lesion should at least decrease in size and have less oedema (less hyperintensity in T2-weighted images), or preferably disappear. If a cystic or heterogenous component is present or develops, the contents of it should not have any enhancement (although its wall may enhance). This subacute form of necrotizing pancreatitis, walled-off necrosis or WON, may contain areas of restricted diffusion in DWI [15]. This should not be interpreted as neoplasia in the absence of contrast enhancement.

During this short follow-up period the inflammation caused by pancreatitis usually settles, but if the suspicious findings persist, endoscopic ultrasound with sampling is the recommended next step in the work-up.

32.6 Groove Pancreatitis

Groove pancreatitis is a relative rare form of pancreatitis, which mainly affects the C-shaped area between the duodenum and head of pancreas, the so called ‘groove’. Groove pancreatitis is also known as cystic dystrophy of the duodenal wall or paraduodenal pancreatitis.

Typical patient with groove pancreatitis is a male in his forties with a heavy alcohol drinking history [16, 17]. Groove pancreatitis may cause obliteration of duodenum causing gastric outlet obstruction, but obstruction of bile duct via stricture or external compression causing obstructive jaundice is more rare. As duodenal stenosis apparently develops slowly, patients have usually lost weight and usually present with abdominal pain. Groove pancreatitis is classified into two forms: Pure form and segmental form.

The pure form of groove pancreatitis is characterized by sheet-like tissue confined in the pancreatic groove that in CT imaging hypoattenuates compared to pancreatic parenchyma. As the tissue is fibrous, delayed enhancement may be seen. The medial duodenal wall may be thickened. In MRI the tissue is hypointense in T1-weighted images and of variable intensity in T2-weighted images. The presence of small T2-hyperintense cysts in the duodenal wall favors the diagnosis.

The segmental form of groove pancreatitis is a more challenging differential from adenocarcinoma, as the fibrous tissue extends into the pancreatic parenchyma and is more mass-like (Fig. 32.4a). It has been suggested that if both the thickening of the duodenal wall and cysts in the area are present, and are accompanied by increased enhancement of the duodenal wall, adenocarcinoma could be fairly certainly excluded [14]. On the other hand, if common bile duct or main pancreatic duct dilatation is present and an abrupt, shouldering cut-off is seen (as opposed to a tapering dilatation), adenocarcinoma should be considered. Brush cytology or biopsy will aid in the diagnosis, but a false negative result due to a fibrotic region of the tumor needs to be considered.

Distinguishing groove pancreatitis from pancreatic cancer may be very difficult radiologically (Fig. 32.4b). Almost one third of patients meeting radiological criteria for groove pancreatitis had in fact pancreatic cancer in a recent series of 38 patients [18]. CA19-9 was equally often elevated in both patient groups, but patients with pancreatic cancer had higher CA19-9 levels than patients with groove pancreatitis (median 270 kU/l versus 44 kU/l). Brush cytology is one of the main cornerstones in differentiating groove pancreatitis from pancreatic cancer, but even so 10% of patients with groove pancreatitis may have suspicious cytology [18]. Differentiating groove pancreatitis from pancreatic cancer is important as large proportion of patients with groove pancreatitis can be managed successfully without surgery [17, 18]. Yet, in a recent systematic review pooling 335 patients with groove pancreatitis from eight studies, 59% underwent surgical treatment, mainly pancreaticoduodenectomy. This might reflect more the fear of pancreatic cancer rather than symptoms or findings necessitating surgery [17]. On the other hand, in one series, 50% of patients with groove pancreatitis did not need any treatment besides pain medication and advice to stop smoking and drinking alcohol [18]. Conservative or endoscopic therapy are the initial treatment of choice in patients without suspicion for pancreatic cancer [19]. In another series, initial treatment was surgical only in 6%, and about three-quarters were treated endoscopically with 70% clinical success rate [20].

32.7 Chronic Pancreatitis

Unlike autoimmune pancreatitis and groove pancreatitis, chronic pancreatitis is usually diagnosed by its distinctive imaging features such as parenchymal and ductal calcifications. If these hallmarks are missing, differentiating chronic pancreatitis from pancreatic cancer may be difficult. Even if diagnosis of chronic pancreatitis

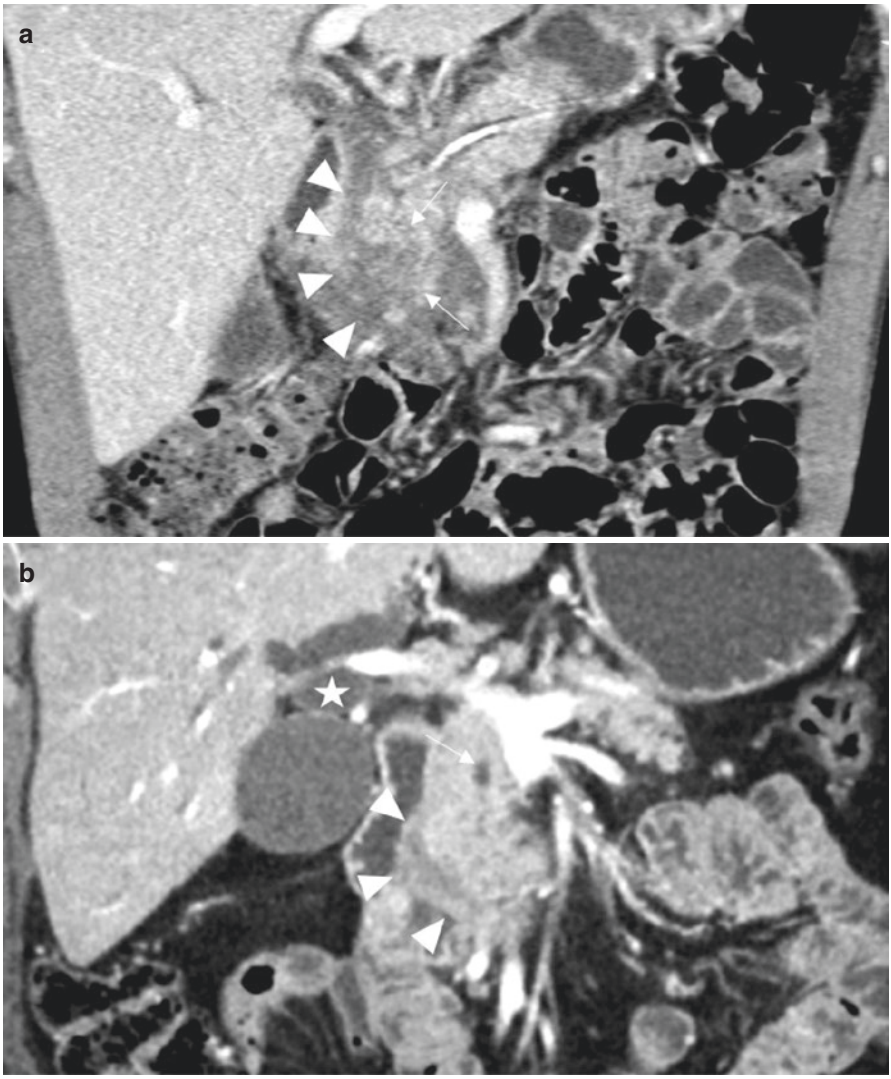

Fig. 32.4 Groove pancreatitis (**a**) and pancreatic adenocarcinoma (**b**). (**a**) Patient in his 40s with symptoms of gastric outlet obstruction and a history of chronic pancreatitis. A hypoenhancing sheet-like mass was seen in the pancreatic groove (arrowheads), with extension into the pancreatic head (arrows) and borderline bile duct obstruction. Pancreaticoduodenectomy was performed and the histology was consistent with groove pancreatitis. (**b**) Patient in her 50s presenting with jaundice. No history of alcohol abuse or pancreatitis. A hypoenhancing sheet-like mass was seen in the pancreatic groove area (arrowheads), causing bile duct (star) and main pancreatic duct (arrow) obstruction. Pancreaticoduodenectomy was performed and the histology was consistent with pancreatic ductal adenocarcinoma

can solidly be made, difficulty remains to diagnose a pancreatic cancer in a patient with chronic pancreatitis. Approximately 1–2% of patients diagnosed with chronic pancreatitis harbor pancreatic cancer instead [21–24]. Further, chronic pancreatitis elevates the risk of developing pancreatic cancer 16-fold after the initial 2 years and threefold after 9 years from diagnosis of chronic pancreatitis [25]. Although this association might be biased by more extensive diagnostics and similar risk factors (alcohol and tobacco) for both diseases, there seems to be a causal relationship through carcinogenic attributes of inflammation [26].

The clinical presentation of chronic pancreatitis is similar to pancreatic cancer: weight loss and upper abdominal pain radiating to the back, and chronic pancreatitis may cause biliary strictures manifesting as jaundice. The radiological diagnosis of pancreatic cancer in a patient with chronic pancreatitis remains a challenge. Inflammation in chronic pancreatitis causes morphological alterations, such as main pancreatic duct and bile duct dilatation, pseudomasses and atrophy of the gland, which are similar to those seen in pancreatic cancer [14]. A pancreatic head mass in chronic pancreatitis should always be investigated for pancreatic cancer. A recent, rather small, series examined the CT findings in patients with both chronic pancreatitis and pancreatic cancer [27]. They concluded that a pancreatic mass is suggestive of pancreatic cancer especially if bile duct was dilatated, acute inflammation was absent, and the mass 'pushed' the pancreatic calcifications aside. Dilatation of main pancreatic duct or atrophy are of little value in differentiating chronic pancreatitis from pancreatic cancer as they occur in both. However, a pancreatic duct is usually more dilated in pancreatic cancer and a mass at the site of obstruction favors cancer diagnosis [28]. The mass in pancreatic cancer does not usually contain ducts, while pseudomass in chronic pancreatitis usually contains ducts. This "duct penetrating sign" is seen in 85% of pseudomasses and often also in other non-neoplastic entities (Fig. 32.2b), but only in 4% of pancreatic cancers [29].

CA19-9 is at the moment the only biomarker available to help distinguishing chronic pancreatitis from pancreatic cancer, but it has approximately 60–80% specificity and sensitivity making both false-negative and false-positive findings a major problem [30].

Endoscopic ultrasound-guided biopsy is one of the cornerstones in differentiating inflammatory mass from pancreatic cancer. EUS fine needle aspiration has very high sensitivity (85%) and specificity (95%) to detect pancreatic cancer in a mass in a normal pancreas, but both of these decrease to a level of 75% in the presence of chronic pancreatitis [31].

The finding that chronic pancreatitis may increase the risk of pancreatic cancer, in addition to the fact that surgery is the most effective treatment modality of symptoms of chronic pancreatitis, makes pancreaticoduodenectomy an appropriate treatment if there is pancreatic head mass or even a slight suspicion of pancreatic cancer in a symptomatic patient with chronic pancreatitis [1, 19].

32.8 Other Solid Malignant Tumours

Pancreatic lymphoma is perhaps one of the most important malignant differential diagnoses for a pancreatic adenocarcinoma, since it may be curable by medical means and does not indicate surgical treatment. Lymphoma's imaging characteristics are to some extent similar to pancreatic cancer and autoimmune pancreatitis: diffuse or segmental masslike enlargement of the pancreas, typically in the head of pancreas that may cause bile and pancreatic duct obstruction (Fig. 32.5) [3]. If pancreatic lymphoma is focal, it is usually well circumscribed. It enhances homogenously, but is hypoattenuating compared to pancreatic parenchyma, and there are no necrotic or calcified areas. In MRI, there is strong diffusion restriction in DWI, comparable to spleen [32]. CA19-9 is usually not elevated, except during biliary obstruction. Elevated lactate dehydrogenase and beta-2 microglobulin are suggestive of lymphoma [33]. Diffusely enlarged pancreas mimics the characteristic sausage-like appearance of autoimmune pancreatitis, and serum IgG4 levels may help to distinguish these two entities. Enlarged lymph nodes that extend below renal vessels are suggestive of a pancreatic lymphoma. Blood vessel encasement does not typically occlude or cause stenosis [3], which is a typical characteristic of lymphoma in general. Endoscopic ultrasound guided sampling is, once again, the cornerstone in achieving the correct diagnosis. If possible, large core needle samples should be obtained to facilitate the histological diagnosis and guide treatment.

Acinar cell carcinoma is a rare malignant neoplasm of pancreas. Less than fifth of cases, acinar cell carcinomas may cause hyperamylasemia/-lipasemia and associated paraneoplastic syndrome with multifocal fat necrosis and polyarthralgia [34]. In majority of cases though, symptoms are similar to pancreatic ductal adenocarcinoma and acinar cell carcinoma is almost as aggressive as pancreatic ductal adenocarcinoma. There are no specific imaging features for acinal cell carcinoma. Its enhancement is usually either hypo- or isovascular compared to pancreatic parenchyma, and it may be capsulated. It may be mistaken for an atypically enhancing neuroendocrine tumor [35]. Usually acinar cell carcinomas are large at presentation, but they usually grow by pushing adjacent structures rather than infiltrating them, making even large tumours resectable contrary to pancreatic ductal adenocarcinoma [34].

Pancreatic metastases are rare, but the most common primary is renal cell carcinoma (Fig. 32.6a). Medical history usually gives clues of such origin, but the delay from the primary cancer to development of pancreatic metastases may be decades. Renal cell carcinomas are nearly indistinguishable radiologically from pancreatic neuroendocrine tumours, but ^{68}Ga somatostatin receptor PET-CT may help in differentiating these [36]. However, also renal cell carcinoma metastases may express somatostatin receptors, resulting in a false positive [37] (Fig. 32.6b) and biopsy confirmation is recommended if the patient has a history of renal cell carcinoma.

Other very rare malignant pancreatic tumours include, hepatoid carcinoma, sarcoma and pancreatoblastoma [38].

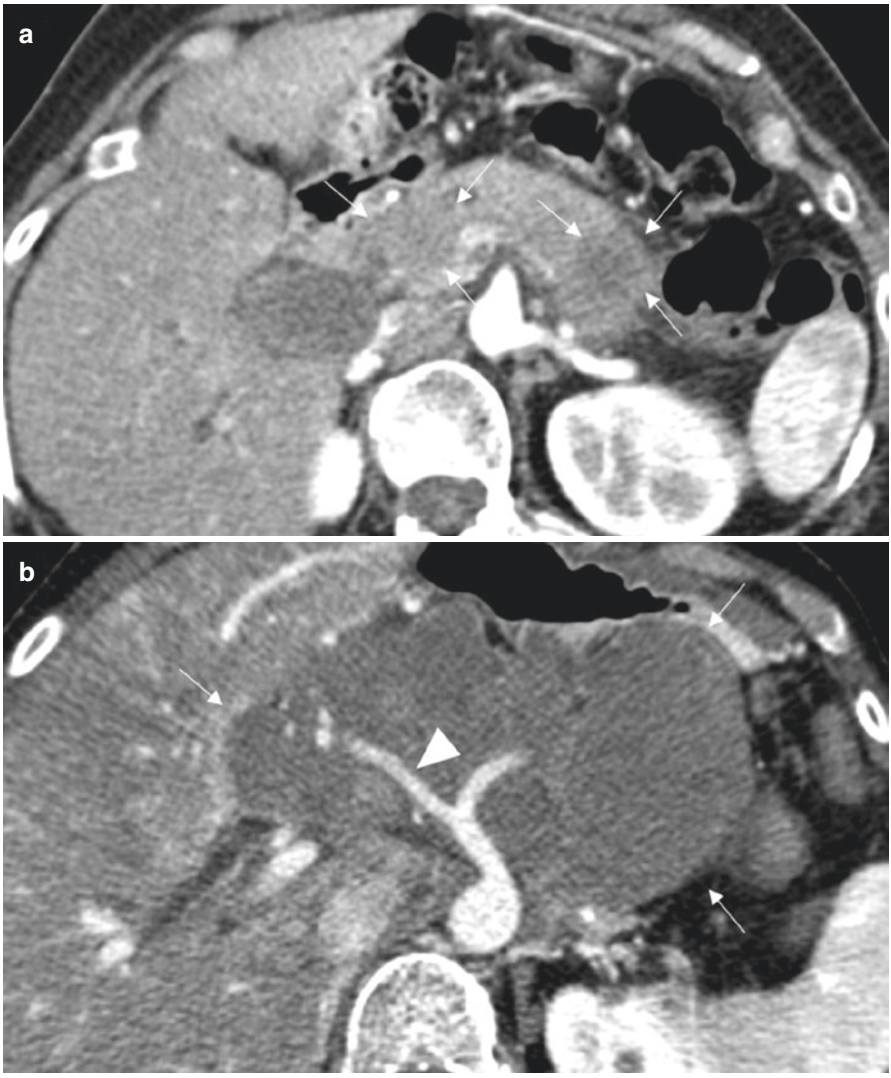

Fig. 32.5 Pancreatic lymphoma. A patient in her 40s presented with upper abdominal pain and jaundice. In CT (**a**) there were two hypodense masses in the pancreatic head and body (arrows). The pancreatic head mass caused biliary dilatation and a slight main pancreatic duct dilatation. Because of patient-related reasons histological sampling was delayed, and in a follow-up CT after 2 months (**b**) the masses had grown considerably (arrows) but did not occlude any vessels (arrowhead, common hepatic artery). There was no evident necrosis. A percutaneous large core needle biopsy was consistent with diffuse large-cell B-cell lymphoma and complete remission was achieved with medical treatment

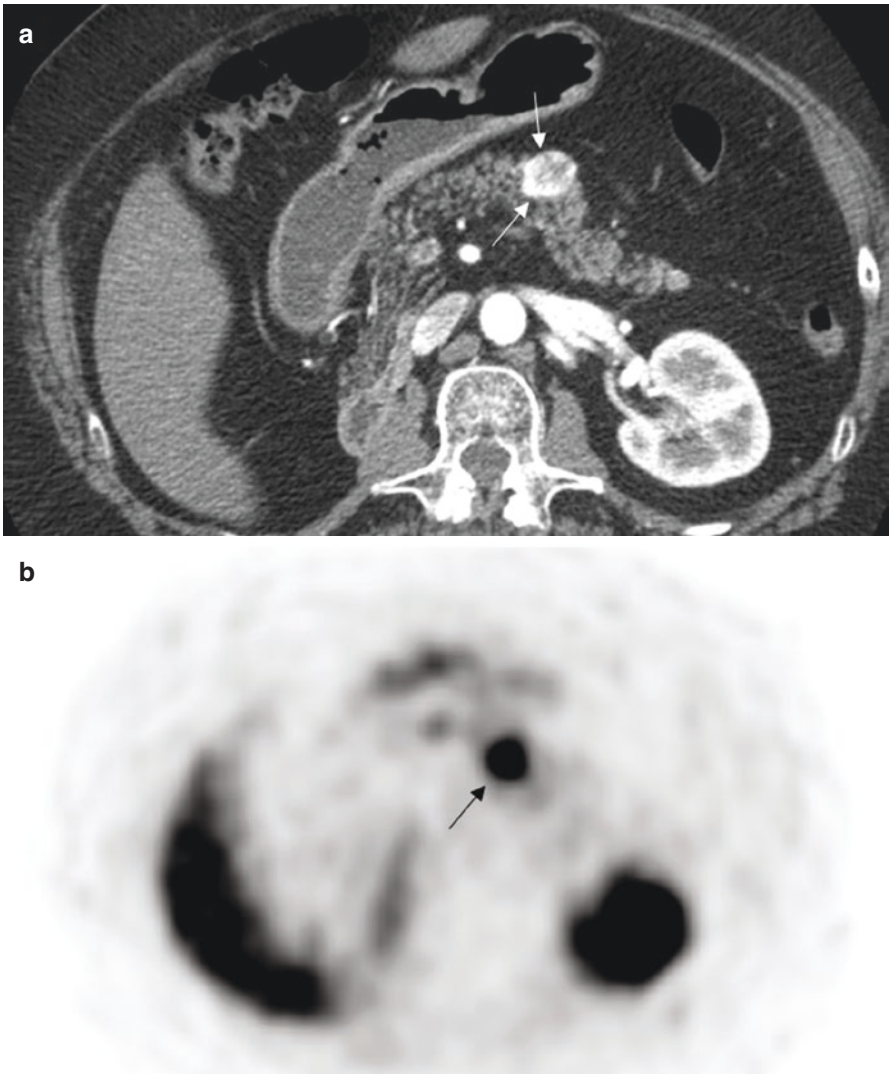

Fig. 32.6 Renal cell carcinoma metastasis. Patient in her 70s with a history of renal cell carcinoma operated 18 years ago. A pancreatic mass was an incidental finding in abdominal ultrasound. In CT (**a**), a hyperenhancing, well-defined mass was seen in the pancreatic body (arrows). In ^{68}Ga somatostatin receptor PET-CT (**b**), the mass showed intense uptake (arrow) suggestive of a neuroendocrine tumor. Distal resection was performed and the histology was consistent with renal clear cell carcinoma metastasis

Table 32.2 Examples of benign solid pancreatic tumours and mimickers

Castleman's disease
Desmoid tumor
Ganglioneuroma
Hemangioma
Leiomyoma
Lipoma
Neurofibroma
Perivascular epithelioid cell tumor
Sarcoidosis
Schwannoma
Solid pseudopapillary tumour
Tuberculosis

32.9 Benign Solid Tumours and Mimickers

A host of very rare benign pancreatic tumors have been described, and detailing each is beyond the scope of this chapter (Table 32.2). In general, benign solid pancreatic neoplasms have a well-defined border, which is the most helpful imaging characteristic when differentiating them from pancreatic adenocarcinoma [39].

Pancreatic lipoma is a rare benign tumour, which usually does not cause any symptoms. They have well defined margins and consist of fat within a thin capsule, which are characteristic imaging findings [40]. Liposarcomas, which are extremely rare, are larger (>5 cm), have irregular and infiltrative margins, have enhancing components, and grow on follow-up. A short follow-up of pancreatic lipoma is recommended to verify its nature [40].

Pancreatic tuberculosis is very rare entity even in endemic areas. The symptoms (weight loss, pain, jaundice), imaging findings, and even C19-9 serology are similar to pancreatic cancer [41]. Pancreatic tuberculosis can present as an abscess, cyst or mass. Endoscopic ultrasound guided sampling of both histological and microbiological samples is the recommended diagnostic strategy. Treatment with standard anti-tubercular therapy for 6–12 months leads to excellent cure rate [41].

Sarcoidosis may uncommonly involve the pancreas. Usually also other manifestations of abdominal sarcoidosis are present, which guides the diagnosis. If sarcoidosis causes mass lesions to the pancreas, they are hypodense in CT imaging and may be multifocal [42].

Other extremely rare mimickers of pancreatic tumour include Castleman's disease and hemangiomas [3, 43].

32.10 Diagnostic Traps

Several normal physiological findings or non-neoplastic conditions may mimic a pancreatic tumor, and unawareness of these entities may lead to unnecessary diagnostic and treatment options [43].

Pancreas is normally lobulated and may sometimes have a single exophytic lobulation that can be mistaken for a tumour. These exophytic lobulas are usually located in the head and neck of pancreas and behave identically to the rest of the pancreas in all imaging modalities [44].

Fatty replacement is a benign process in which pancreatic tissue is replaced by fat tissue. Usually whole gland is affected, but the replacement may be focal or focally absent (Fig. 32.7). Fatty replacement lacks mass effect, does not affect duct or vascular structures and does not alter the contour of the pancreas [45]. It typically spares the parenchyma immediately adjacent to the intrapancreatic common bile duct. Focal fatty replacement may sometimes mimic a hypodense tumor especially in CT imaging, but an MRI with in-phase/out-of-phase imaging, revealing fat content in tissue, is helpful [46].

Intrapancreatic accessory spleen is a congenital benign anomaly usually located in the pancreatic tail, and is found in approximately 2% of the population [47]. It is usually, as other splenic tissue, hyperdense in CT imaging and often mislabeled as

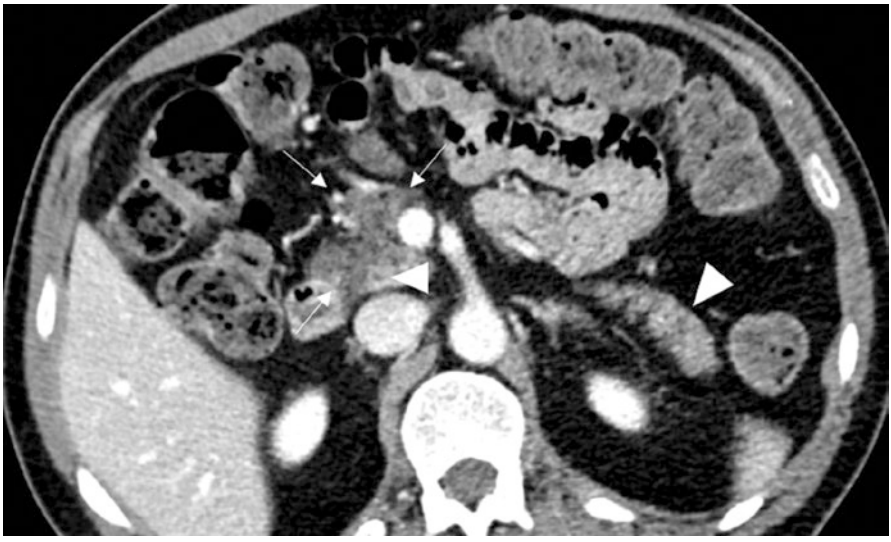

Fig. 32.7 Focal fatty infiltration. Patient in his 60s with colorectal carcinoma had an incidental finding of hypoattenuating tissue in the pancreatic head. The CT features are consistent with focal fatty infiltration: a large irregular hypoattenuating area in which the lobular structure is still visible (arrows), no duct or vessel obstruction, sparing of the tissue around the intrapancreatic common bile duct in which the attenuation is similar to the normal pancreatic tail (arrowheads). In a 2-year follow-up CT, there was no change in the appearance of the pancreatic head

pancreatic neuroendocrine tumour [47]. Unfortunately, the neuroendocrine tumour imaging gold standard ^{68}Ga somatostatin receptor PET-CT is not helpful, as normal splenic tissue is also positive for somatostatin receptors [37] (Fig. 32.6b). A SPECT-CT with technetium 99m-labelled heat-damaged red blood cells can be used to differentiate the two entities [48].

32.11 Conclusions

In the majority of the patients presenting with a pancreatic tumor, the diagnosis is obtainable by routine work-up using computed tomography, CA19-9 and possibly ERC with brush cytology. Some patients require extensive work-up, and yet solid diagnosis might not be reached. Threshold for pancreaticoduodenectomy may be kept low in symptomatic patients with chronic pancreatitis and a head lesion even in the absence of histological verification. IgG4 levels and a biopsy should be obtained in patients with findings suggestive of autoimmune pancreatitis. CA19-9 levels are useful in the differential diagnostics of pancreatic cancer and autoimmune, groove and chronic pancreatitis, but interpretation must be based on clinical presentation, radiological findings instead of CA19-9 alone. Rare mimickers of pancreatic tumour must be kept in mind to avoid unnecessary treatments. In cases where unequivocal diagnosis cannot be obtained, pancreatic surgery could still be recommended if malignancy is suspected, but this needs to be carefully discussed with the patient and make a shared-decision balancing the risks and benefits of all options. Hopefully ongoing research will help clinicians and patients in such cases in the future.

References

1. Asbun HJ, Conlon K, Fernández-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155:887–92.
2. Zhang L, Smyrk TC. Autoimmune pancreatitis and IgG4-related systemic diseases. Int J Clin Exp Pathol. 2010;3:491–504.
3. Sandrasegaran K, Tomasian A, Elsayes KM, Nageswaran H, Shaaban A, Shanbhogue A, Menias CO. Hematologic malignancies of the pancreas. Abdom Imaging. 2015;40:411–23.
4. Kamisawa T, Chari ST, Giday SA, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas. 2011;40:809–14.
5. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7:1097–103.
6. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
7. Hafezi-Nejad N, Singh VK, Fung C, Takahashi N, Zaheer A. MR imaging of autoimmune pancreatitis. Magn Reson Imaging Clin N Am. 2018;26:463–78.

8. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol. 2007;102:1646–53.
9. Chang M-C, Liang P-C, Jan S, Yang C-Y, Tien Y-W, Wei S-C, Wong J-M, Chang Y-T. Increase diagnostic accuracy in differentiating focal type autoimmune pancreatitis from pancreatic cancer with combined serum IgG4 and CA19-9 levels. Pancreatology. 2014;14:366–72.
10. van Heerde MJ, Buijs J, Hansen BE, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. Dig Dis Sci. 2014;59:1322–9.
11. van Heerde MJ, Biermann K, Zondervan PE, Kazemier G, van Eijck CHJ, Pek C, Kuipers EJ, van Buuren HR. Prevalence of autoimmune pancreatitis and other benign disorders in pancreatoduodenectomy for presumed malignancy of the pancreatic head. Dig Dis Sci. 2012;57:2458–65.
12. de Castro SMM, De Nes LCF, Nio CY, Velseboer DC, Ten Kate FJW, Busch ORC, van Gulik TM, Gouma DJ. Incidence and characteristics of chronic and lymphoplasmacytic sclerosing pancreatitis in patients scheduled to undergo a pancreatoduodenectomy. HPB (Oxford). 2010;12:15–21.
13. Frampas E, Morla O, Regenet N, Eugène T, Dupas B, Meurette G. A solid pancreatic mass: tumour or inflammation? Diagn Interv Imaging. 2013;94:741–55.
14. Kothari K, Vendrami CL, Kelahan LC, Shin JS, Mittal P, Miller FH. Inflammatory mimickers of pancreatic adenocarcinoma. Abdom Radiol. 2019;45:1387–96.
15. Sandrasegaran K, Heller MT, Panda A, Shetty A, Menias CO. MRI in acute pancreatitis. Abdom Radiol. 2019;144:1252–11.
16. Stolte M, Weiss W, Volkholz H, Rösch W. A special form of segmental pancreatitis: “groove pancreatitis”. Hepato-Gastroenterology. 1982;29:198–208.
17. Kager LM, Lekkerkerker SJ, Arvanitakis M, Delhaye M, Fockens P, Boermeester MA, van Hooft JE, Besselink MG. Outcomes after conservative, endoscopic, and surgical treatment of groove pancreatitis: a systematic review. J Clin Gastroenterol. 2017;51:749–54.
18. Lekkerkerker SJ, Nio CY, Issa Y, et al. Clinical outcomes and prevalence of cancer in patients with possible groove pancreatitis. J Gastroenterol Hepatol. 2016;31:1895–900.
19. Dominguez-Munoz JE, Drewes AM, Lindkvist B, Ewald N, Czakó L, Rosendahl J, Löhr JM, HaPanEU/UEG Working Group. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. Pancreatology. 2018;18:847–54.
20. Arvanitakis M, Rigaux J, Toussaint E, et al. Endotherapy for paraduodenal pancreatitis: a large retrospective case series. Endoscopy. 2014;46:580–7.
21. Munigala S, Kanwal F, Xian H, Agarwal B. New diagnosis of chronic pancreatitis: risk of missing an underlying pancreatic cancer. Am J Gastroenterol. 2014;109:1824–30.
22. Karlson BM, Ekbom A, Josefsson S, McLaughlin JK, Fraumeni JF, Nyrén O. The risk of pancreatic cancer following pancreatitis: an association due to confounding? Gastroenterology. 1997;113:587–92.
23. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg Å, Domellöf L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med. 1993;328:1433–7.
24. Talamini G, Bassi C, Falconi M, et al. Early detection of pancreatic cancer following the diagnosis of chronic pancreatitis. Digestion. 1999;60:554–61.
25. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol. 2017;112:1366–72.
26. Hausmann S, Kong B, Michalski C, Erkan M, Friess H. The role of inflammation in pancreatic cancer. Adv Exp Med Biol. 2014;816:129–51.
27. Mohamed A, Ayav A, Belle A, Orry X, Chevaux J-B, Laurent V. Pancreatic cancer in patients with chronic calcifying pancreatitis: computed tomography findings - a retrospective analysis of 48 patients. Eur J Radiol. 2017;86:206–12.
28. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. 2014;43:1143–62.

29. Ichikawa T, Sou H, Araki T, Arbab AS, Yoshikawa T, Ishigame K, Haradome H, Hachiya J. Duct-penetrating sign at MRCP: usefulness for differentiating inflammatory pancreatic mass from pancreatic carcinomas. Radiology. 2001;221:107–16.
30. Su S-B, Qin S-Y, Chen W, Luo W, Jiang H-X. Carbohydrate antigen 19-9 for differential diagnosis of pancreatic carcinoma and chronic pancreatitis. World J Gastroenterol. 2015;21:4323–33.
31. Narkhede RA, Desai GS, Prasad PP, Wagle PK. Diagnosis and management of pancreatic adenocarcinoma in the background of chronic pancreatitis: core issues. Dig Dis. 2019;37:315–24.
32. Manning MA, Paal EE, Srivastava A, Mortele KJ. Nonepithelial neoplasms of the pancreas, Part 2: Malignant tumors and tumors of uncertain malignant potential from the radiologic pathology archives. Radiographics. 2018;38:1047–72.
33. Anand D, Lall C, Bhosale P, Ganeshan D, Qayyum A. Current update on primary pancreatic lymphoma. Abdom Radiol. 2016;41:347–55.
34. Chaudhary P. Acinar cell carcinoma of the pancreas: a literature review and update. Indian J Surg. 2015;77:226–31.
35. Raman SP, Hruban RH, Cameron JL, Wolfgang CL, Kawamoto S, Fishman EK. Acinar cell carcinoma of the pancreas: computed tomography features--a study of 15 patients. Abdom Imaging. 2013;38:137–43.
36. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68) Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. Am J Nucl Med Mol Imaging. 2014;4:426–34.
37. Rufini V, Inzani F, Stefanelli A, Castaldi P, Perotti G, Cinquino A, Indovina L, Rindi G. The accessory spleen is an important pitfall of 68Ga-DOTANOC PET/CT in the workup for pancreatic neuroendocrine neoplasm. Pancreas. 2017;46:157–63.
38. Shetty AS, Menias CO. Rare pancreatic tumors. Magn Reson Imaging Clin N Am. 2018;26:421–37.
39. Manning MA, Srivastava A, Paal EE, Gould CF, Mortele KJ. Nonepithelial neoplasms of the pancreas: radiologic-pathologic correlation, Part 1--Benign tumors: from the radiologic pathology archives. Radiographics. 2016;36:123–41.
40. Butler JR, Fohtung TM, Sandrasegaran K, Ceppa EP, House MG, Nakeeb A, Schmidt CM, Zyromski NJ. The natural history of pancreatic lipoma: does it need observation. Pancreatology. 2016;16:95–8.
41. Sharma V, Rana SS, Kumar A, Bhasin DK. Pancreatic tuberculosis. J Gastroenterol Hepatol. 2016;31:310–8.
42. Warshauer DM, Lee JKT. Imaging manifestations of abdominal sarcoidosis. AJR Am J Roentgenol. 2004;182:15–28.
43. Torres US, Matsumoto C, de Macedo Neto AC, Caldana RP, Motoyama Caiado ÂH, Tiferes DA, Warmbrand G, de Godoy LL, D'Ippolito G. Common and uncommon benign pancreatic lesions mimicking malignancy: imaging update and review. Semin Ultrasound CT MR. 2018;39:206–19.
44. Ross BA, Jeffrey RB, Mindelzun RE. Normal variations in the lateral contour of the head and neck of the pancreas mimicking neoplasm: evaluation with dual-phase helical CT. AJR Am J Roentgenol. 1996;166:799–801.
45. Kawamoto S, Siegelman SS, Bluemke DA, Hruban RH, Fishman EK. Focal fatty infiltration in the head of the pancreas: evaluation with multidetector computed tomography with multiplanar reformation imaging. J Comput Assist Tomogr. 2009;33:90–5.
46. Kim HJ, Byun JH, Park SH, Shin YM, Kim PN, Ha HK, Lee M-G. Focal fatty replacement of the pancreas: usefulness of chemical shift MRI. Am J Roentgenol. 2007;188:429–32.
47. Spencer LA, Spizarny DL, Williams TR. Imaging features of intrapancreatic accessory spleen. Br J Radiol. 2010;83:668–73.
48. Barber TW, Dixon A, Smith M, Yap KSK, Kalff V. Ga-68 octreotate PET/CT and Tc-99m heat-denatured red blood cell SPECT/CT imaging of an intrapancreatic accessory spleen. J Med Imaging Radiat Oncol. 2016;60:227–9.

Chapter 33
The Multidisciplinary Team Conference

Jakob Kirkegård and Frank Viborg Mortensen

Take Home Messages

- The multidisciplinary team conference is an integrated part of pancreatic cancer diagnostics
- A correct tumor staging and resectability assessment is pivotal to make informed recommendations on treatment allocation
- Tumor staging and resectability assessment varies substantially between centers despite existence of international guidelines
- No evidence of a positive impact of multidisciplinary team conferences on survival exists

Future Perspectives

- Do the multidisciplinary team conferences improve pancreatic cancer survival?
- Do the perceived benefit of multidisciplinary team conferences justify the additional costs and resource demands?
- Can the multidisciplinary team conference infrastructure be used to increase inclusion rates in clinical trials?
- What is the most optimal constellation for a multidisciplinary team conference in terms of group dynamics and leadership roles?
- Should a national/second-opinion multidisciplinary team conference be universal?
- Should geriatricians and dietician be a part of multidisciplinary team conference?

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33.1 History of the Multidisciplinary Team Conference

Multidisciplinary team conferences have existed for the last 50 years in the United States, where it is often referred to as tumor boards. They were originally introduced for educational purposes rather than optimizing patient care [1]. In the last two decades, however, there has been a shift in focus for multidisciplinary team conferences towards optimizing patient work-up, tumor staging, and treatment. The transition started in the United Kingdom in the late 1990s driven by public and political pressure after a series of reports demonstrating pronounced regional variations in treatment of cancer patients [2]. Soon after, similar multidisciplinary team conferences started in other Western countries [3, 4]. Especially two ways to organize multidisciplinary team conferences have become widespread. In the United States, many institutions prefer what is often called "one-step care", in which patients at a given day is examined by all members of the multidisciplinary tumor board and a personal plan is designed after group discussion [5]. In Europe, Australia, and Canada, several patients are typically evaluated at multidisciplinary team conferences and plans for eventually further work-up, staging, and treatment are decided [5].

33.2 Purpose of the Multidisciplinary Team Conference

The central purpose of the multidisciplinary team conference is to conduct an accurate staging of each patient's tumor (Fig. 33.1).

A correct tumor staging including resectability assessment is pivotal and the main determinant of treatment allocation and thus the patient's prognosis. In patients with a small tumor confined to the pancreas, and in patients with metastatic lesions, this assessment is often straightforward, i.e. surgery if performance allows it and oncological treatment/best supportive care, respectively. However, in about one-third of the patients, the tumor has grown outside of the pancreas but has not yet metastasized [6]. In these patients with more advanced tumors, tumor staging and resectability assessment can be particularly challenging.

33.3 Participants at the Multidisciplinary Team Conference

Usually, participants at the multidisciplinary team conference include surgeons/surgical oncologists, radiologists, medical oncologists, gastroenterologists, and pathologists. There are, however, no uniform requirements of which medical specialties should be represented for a conference to be considered as "multidisciplinary team conference". To conduct an evaluation of surgical resectability of a pancreatic cancer tumor, a radiologist and a surgeon/surgical oncologist seem to be the minimum

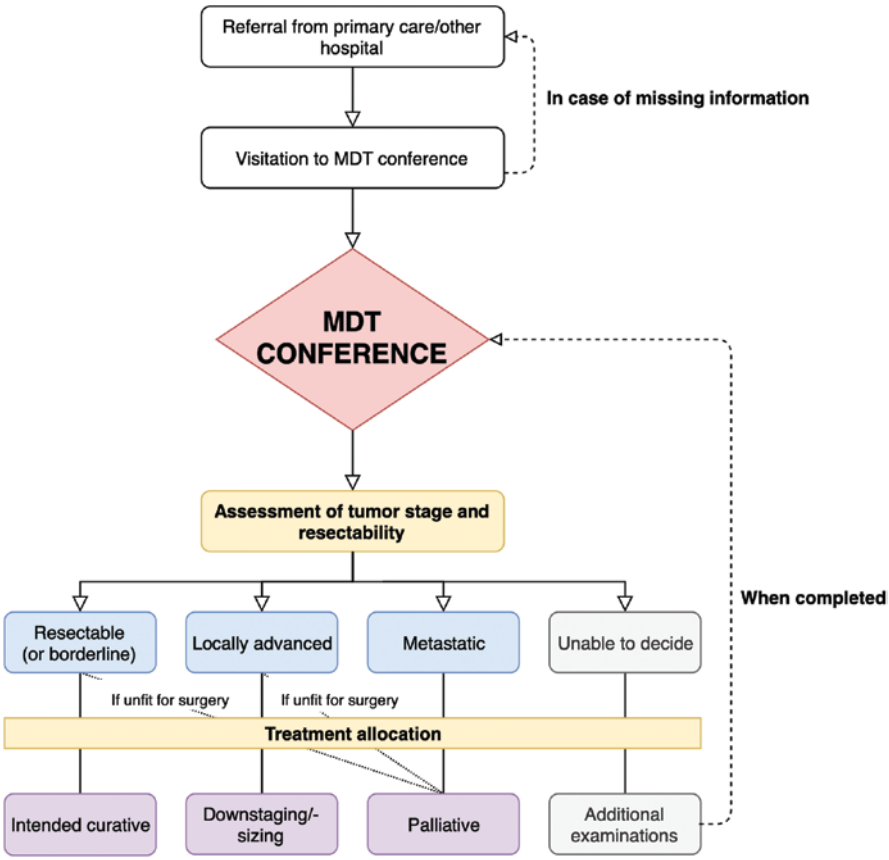

Fig. 33.1 A tentative work-flow for multidisciplinary team conferences. MDT denotes "multidisciplinary team"

requirement. To supply with important knowledge on potential medical oncological treatment options, a medical oncologist should be present as well. Participation of clinical nurse specialists with an overview of each patient and their path through the healthcare system is likely to support the decision-making process in multidisciplinary team conferences [7].

33.4 The Decision-Making Process and Group Dynamics

Multidisciplinary team conferences are shown to have a positive effect on the decision-making process, which is a likely explanation of the widespread use of these. Factors known to impact the decision-making process may include *e.g.* presence of a physician with prior knowledge of the patient, time pressure, absence of

medical specialists, and lack of leadership [8, 9]. Leadership in the multidisciplinary team conference varies across different centers. In some places, the conference is led by a radiologist presenting the images, whereas other institutions may have a surgeon as the leader. To improve efficiency of the decision-making process—as in the case of the multidisciplinary team conference—a strong hierarchy may be preferable but is not without challenges. Although a clear leadership seems to be an important factor in the decision-making process [9], having too many people of high power in the same conference is likely to impair the decision-making process. A strong hierarchy may not be required at all, as the members of the multidisciplinary team conference are able to reach consensus in more than 90% of the cases by panel discussion [10].

33.5 Efficiency of the Multidisciplinary Team Conference

A combination of a growing number of treatment options and an increasing level of comorbidities highlights the importance of an effective and thorough discussion of each case. However, a growing cancer incidence worldwide may lead to decision-fatigue during the multidisciplinary team meetings, and excessive work burdens have been identified to impair the quality of the decision-making process [10]. As such, the number of cases discussed at each meeting should be limited to a reasonable amount. To reduce the work load, it is important that all necessary material is available to the multidisciplinary team board, *e.g.* assert that scans are of sufficient quality and that a proper medical history is available. Around 10% of all recommendations from the multidisciplinary team conference are never carried out, which may be due to comorbidities precluding curative-intent surgery or patient preferences that the multidisciplinary team board were not informed of (Box 33.1) [10].

Box 33.1 What Is Required to Reach a Decision at the Multidisciplinary Team Conference?

NEED TO HAVE

- Patient age
- Relevant comorbidity and medical history
- Updated and sufficient imaging
- Contact information on referring physician

NICE TO HAVE

- Information on whether the patient is fit for major surgery
- Patient preference
- Previous antineoplastic treatment
- Histology reports
- Information on relevant genetic mutations

33.6 Pancreatic Cancer Staging and Assessment of Resectability

Pancreatic cancer is staged according to the tumor-node-metastasis (TNM) classification, 8th edition. This classification is used to assess the local extent of the tumor (T), spread to the lymph nodes (N), and presence of metastases (M). Compared with the 7th edition, the N-status is now classified as N0, N1, or N2 instead of N0 and N1, as not only the presence—but also number—of positive lymph nodes are predictors of prognosis [11]. Based on the TNM stage, the American Joint Committee on Cancer (AJCC) stage can be mapped [12]. The AJCC stage is an important guide to decide on treatment allocation, as survival outcomes are largely dependent on stage.

In addition to staging of the tumor, the multidisciplinary team conference must recommend a treatment allocation, based on the resectability assessment. Resectability assessment is strongly correlated with tumor invasion of central vascular structures, such as the celiac axis, hepatic artery, and the superior mesenteric artery. In principle, the resectability assessment performed at the multidisciplinary team conference can fall into four categories (Box 33.2) [13]. In addition to anatomical factors (vascular invasion), the tumor can also be assessed as borderline resectable based on biological (e.g. level of CA19-9) or conditional (performance status or comorbidities) factors [14]. In patients with borderline resectable tumors, there is considerable variation in the treatment allocation [15]. Despite the existence of international consensus guidelines on determining resectability in pancreatic cancer from organizations such as the National Comprehensive Network [16], Americas Hepato-Pancreato-Biliary Association [17], or the Japan Pancreas Society [18], a substantial variation in resectability assessment has been documented. For example, a study of 19 pancreatic cancer patients assessed at seven different multidisciplinary team conferences found that the decision on resectability was identical in only half of the cases [15] (Fig. 33.2). This discordance may be due to local traditions and competences and clearly demonstrates the impact of local traditions and competences.

Box 33.2 Resectability Assessment

RESECTABLE

The tumor is free of central vascular structures and the patient is likely to benefit from surgery.

BORDERLINE RESECTABLE

Invasion of central vascular structures that do not preclude curative-intent surgery

LOCALLY ADVANCED

Invasion of central vascular structures that preclude upfront curative-intent surgery

METASTATIC

The tumor has metastasized beyond the pancreas

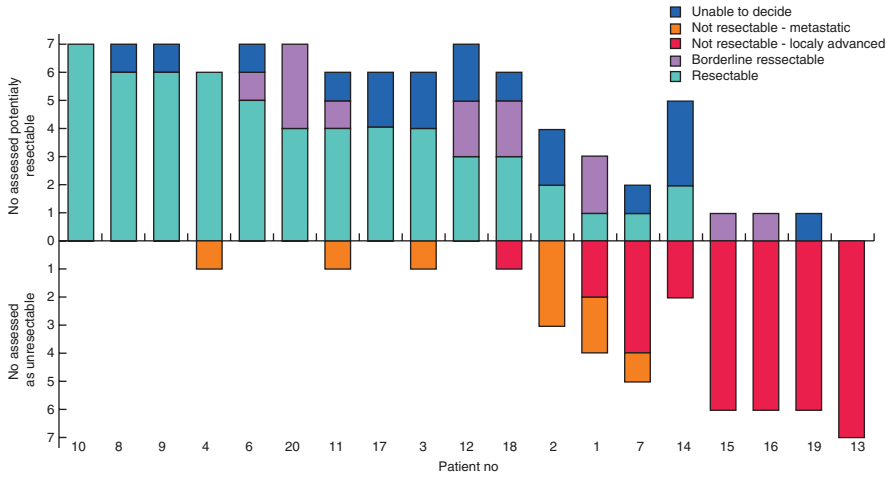

Fig. 33.2 Agreement of resectability across several MDTs. Resectability assessment of 19 patients with pancreatic cancer at seven different multidisciplinary team conferences. (Reprinted with permission from British Journal of Surgery, Kirkegård et al. Multicentre study of multidisciplinary team assessment of pancreatic cancer resectability and treatment allocation. Br J Surg. 2019;106(6):756–764)

33.7 Impact of Multidisciplinary Team Conferences

Despite widespread implementation of multidisciplinary team conferences, their impact on real-world outcomes are largely unknown. Generally, patients discussed at a multidisciplinary team conference have shown to be more satisfied and more often get a correct diagnosis and treatment allocation according to available guidelines [19], but no effect on survival has been shown.

A Norwegian study found that patients living in counties where multidisciplinary team conferences were implemented had improved survival compared with patients in counties without multidisciplinary team conferences, and suggested that this could be explained by more frequent use of chemotherapy in the former group [20]. There is an urgent need for research on the impact of the multidisciplinary team conference on survival of pancreatic cancer patients. One study of 355 patients with malignant or benign pancreatic mass lesions evaluated at a single institution found that review of the patient files at the multidisciplinary team conference changed the proposed treatment allocation from surgery to non-surgical treatment in 25% of the patients [21]. These findings agree with another study of 203 patients with pancreatic cancer, of which 19% had their treatment allocation changed following evaluation at the multidisciplinary team conference [22]. Of these patients, 75% went from surgical to non-surgical treatment, mainly as a result of increased detection of distant metastases. As surgical treatment will not benefit patients with metastatic lesions, these findings emphasize the importance of a thorough multidisciplinary workup to avoid futile surgery.

33.8 Perspectives of Multidisciplinary Team Conferences

The widespread use of multidisciplinary team conferences may confer additional benefits to patients beyond correct diagnosis and optimal treatment allocation. Use of multidisciplinary team conferences could facilitate an infrastructure of patient inclusion in clinical trials, which can assist researchers and clinicians in bringing forward pancreatic cancer research. Furthermore, evaluation of patients in multidisciplinary team conferences can also increase the number of patients receiving more aggressive antineoplastic treatment [23], which may again increase survival albeit at a potential cost of reduced quality of life.

Another aspect of multidisciplinary team conference is related to centralization. It is still debatable which hospitals should have multidisciplinary team conferences, and if extremely specialized multidisciplinary team conferences may improve patient outcome. For example, a national multidisciplinary team conference was implemented in Denmark in early 2019. The rationale for this conference was the large variation in tumor staging and differences in survival according to geographical residency [15, 24]. At this conference, which is conducted weekly using a videocall, participants from all centers in Denmark performing pancreatic cancer surgery mutually assess all patients with non-metastatic tumors who were considered unresectable at the local multidisciplinary team conference. Thus, this national multidisciplinary team conference serves as a systematic second-opinion system for all patients with borderline resectable or locally advanced pancreatic cancers. A similar conference has also been implemented in Sweden. Results from these national multidisciplinary team conferences are still awaited.

Other open questions related to the multidisciplinary team conference remains. For example, to deal with the increasing burden of cancer in the elderly, geriatricians may play a central role of the multidisciplinary team conferences in longer terms. With increasing availability of genome sequencing, personalized medicine may become increasing used at the multidisciplinary team conferences, and clinical geneticists could play a role at the multidisciplinary team conference. Also, prehabilitation prior to pancreatic surgery can optimize postoperative outcomes [25], suggesting that clinical dieticians and physiotherapists should be a more integrated part of multidisciplinary team conferences.

33.9 The Multidisciplinary Team Conference in Education and Patient Involvement

The multidisciplinary team conference provides a plethora of possibilities for teaching and education. Residents, fellows, and medical students can learn a lot from these conferences and are perfectly capable to present cases themselves, although their input may be limited. The multidisciplinary team conference can improve the younger colleagues' skills in concise presentation of cases and strengthen their

clinical knowledge as well as their professional skills and ability to work as a team. Patient involvement at the multidisciplinary team conference are widely debated. A Danish study of patients with ear-nose-throat cancer found that in more than half of the cases, patient participation contributed to a change in the treatment allocations involving reduced use of oncological treatment due to performance status and complete abstinence of anti-neoplastic treatment due to patient preferences [26]. In this study, each patient was allocated a timeframe of 45 min. While this may seem long, surgeons were in general positive towards patient involvement, as it inferred fewer cancelled operations and a more efficient patient flow [26]. Patient involvement at the multidisciplinary team conference may thus seem as a positive initiative, but it is also associated with substantial logistical challenges.

33.10 Future Research

No randomized studies examining the impact of multidisciplinary team conferences on cancer survival have been performed. In order to perform a cost-benefit analysis of the value of multidisciplinary team conferences, studies to examine a potential survival benefit are crucial. Furthermore, while only inter-observer variation has been investigated, no studies to date have analyzed intra-observer variance.

References

1. Berman HL. The tumor board: is it worth saving? Mil Med. 1975;140:529–31.
2. Calman-Hine Report. Expert Advisory Group on Cancer. A policy framework for commissioning cancer services: a report to the chief medical officers of England and Wales. London: Department of Health; 1995.
3. van Leeuwen AF, Voogt E, Visser A, van der Rijt CC, van der Heide A. Considerations of healthcare professionals in medical decision-making about treatment for clinical end-stage cancer patients. J Pain Symptom Manag. 2004;28:351–5.
4. van Nes JG, van de Velde CJ. [The multidisciplinary breast cancer care team: promoting better care]. Ned Tijdschr Geneeskd. 2005;149:1929–1931.
5. Prades J, Remue E, van Hoof E, Borras JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Policy. 2015;119:464–74.
6. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7:e1000267.
7. Wallace I, Barratt H, Harvey S, Raine R. The impact of Clinical Nurse Specialists on the decision making process in cancer multidisciplinary team meetings: a qualitative study. Eur J Oncol Nurs. 2019;43:101674.
8. Basta YL, Baur OL, van Dieren S, Klinkenbijl JH, Fockens P, Tytgat KM. Is there a benefit of multidisciplinary cancer team meetings for patients with gastrointestinal malignancies? Ann Surg Oncol. 2016;23:2430–7.
9. Lanceley A, Savage J, Menon U, Jacobs I. Influences on multidisciplinary team decision-making. Int J Gynecol Cancer. 2008;18:215–22.

10. Jalil R, Ahmed M, Green JS, Sevdalis N. Factors that can make an impact on decision-making and decision implementation in cancer multidisciplinary teams: an interview study of the provider perspective. Int J Surg. 2013;11:389–94.
11. van Roessel S, Kasumova GG, Verheij J, et al. International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg. 2018;153:e183617.
12. Edge SB, Byrd DR, Compton CG, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Handbook. 7th ed. New York, NY: Springer; 2010.
13. National MDT conference for pancreatic cancer. 2019. Danish Board of Health, Copenhagen.
14. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18:2–11.
15. Kirkegard J, Aahlin EK, Al-Saiddi M, et al. Multicentre study of multidisciplinary team assessment of pancreatic cancer resectability and treatment allocation. Br J Surg. 2019;106:756–64.
16. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
17. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16:1727–33.
18. Yamada S, Fujii T, Takami H, et al. Evaluation and proposal of novel resectability criteria for pancreatic cancer established by the Japan Pancreas Society. Surgery. 2017;162:784–91.
19. Basta YL, Bolle S, Fockens P, Tytgat K. The value of multidisciplinary team meetings for patients with gastrointestinal malignancies: a systematic review. Ann Surg Oncol. 2017;24:2669–78.
20. Kersten C, Cvancarova M, Mjaland S, Mjaland O. Does in-house availability of multidisciplinary teams increase survival in upper gastrointestinal-cancer? World J Gastrointest Oncol. 2013;5:60–7.
21. Brauer DG, Strand MS, Sanford DE, et al. Utility of a multidisciplinary tumor board in the management of pancreatic and upper gastrointestinal diseases: an observational study. HPB (Oxford). 2017;19:133–9.
22. Pawlik TM, Laheru D, Hruban RH, et al. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. Ann Surg Oncol. 2008;15:2081–8.
23. Brannstrom F, Bjerregaard JK, Winbladh A, et al. Multidisciplinary team conferences promote treatment according to guidelines in rectal cancer. Acta Oncol. 2015;54:447–53.
24. Kirkegard J, Ladekarl M, Fristrup CW, Hansen CP, Sall M, Mortensen FV. Urban versus rural residency and pancreatic cancer survival: a Danish nationwide population-based cohort study. PLoS One. 2018;13:e0202486.
25. Nakajima H, Yokoyama Y, Inoue T, et al. Clinical benefit of preoperative exercise and nutritional therapy for patients undergoing hepato-pancreato-biliary surgeries for malignancy. Ann Surg Oncol. 2019;26:264–72.
26. Patient involvement in MDT conferences. Copenhagen: Danish Cancer Society; 2018.

Chapter 34
Gross Evaluation and Histopathology

Eline C. Soer and Caroline Sophie Verbeke

Take Home Messages

- Specimen dissection, macroscopic examination, and tissue sampling are key determinants of the quality of the pathology reporting on surgical pancreatic cancer specimens. Standardization of this part of the pathology examination is essential for comparability of data.
- Pancreatic ductal adenocarcinoma is characterized by a high stromal content and a dispersed growth pattern. While the former presents a severe obstacle to bulk molecular analysis, the latter results in frequent underestimation of tumour size and extent, both during macroscopic examination and on preoperative imaging.
- Reporting of pancreatic cancer specimens following neoadjuvant treatment is challenging, because tumour regression is often patchy and viable residual cancer cannot be confidently distinguished from fibrosis by naked-eye inspection. Consequently, tissue sampling must be extensive, and assessment of residual tumour size and ypT-stage is difficult and liable to interobserver variation. Existing tumour regression grading systems are of limited prognostic value and fraught with interobserver variation.

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Future Perspectives

- Ductal adenocarcinoma shows a wide range of histomorphological variation that requires investigation, including its relation with current molecular taxonomy models and relevance regarding the effect of chemotherapy.
- Currently, pathology examination is limited to assessing the extent, spread, and grade of differentiation of the cancer cell component of the tumour. Functional aspects of the cancer (e.g., proliferation rate, expression of chemosensitivity markers) and features of the tumour stroma that may have an impact on treatment success and patient outcome should be considered, both for treatment-naive and neoadjuvantly treated pancreatic cancers.

34.1 Introduction

Pancreatic ductal adenocarcinoma is associated with poor patient outcome. The key determinants of the tumour's aggressive biology are readily appreciated on microscopic examination and represent the hallmarks of this cancer: (1) a highly infiltrative and dispersed growth, (2) an exceedingly prominent stroma, and (3) marked morphological heterogeneity. While the first feature directly relates to the size of the tumour and T-stage, the latter two are currently not part of the pathology reporting data set.

The aim of routine pathology examination of surgical pancreatic resection specimens is first and foremost to confirm the diagnosis, in particular the cancer origin (pancreas versus ampulla, common bile duct, or duodenum) and the exact histological tumour entity, that is, ductal adenocarcinoma or any of its subtypes [1]. Furthermore, the main tissue-based prognostic predictors are assessed according to the principles of TNM-staging along with additional findings, such as lymphovascular tumour propagation and margin status, which have a smaller prognostic impact [2, 3]. For these core data to be comparable between centres and studies, pathology examination should be fully standardized. Unfortunately, despite efforts to that effect, an international consensus has not been reached yet. While current national guidelines and international data sets for the reporting of pancreatic cancer aim at standardizing the *recording* of the data items [4–7], the macroscopic and microscopic *examination procedures* that are required to obtain these data, have been left largely to the discretion of the individual pathologist and, consequently, vary between centres [8–10].

Key steps in the gross examination of pancreatic resection specimens and data items that are gleaned during microscopic examination are described below, along with their clinical relevance and possible pitfalls or shortcomings.

34.2 Macroscopic Examination

Macroscopic examination consists of specimen dissection, naked-eye inspection, and tissue sampling. It is this part of the pathology examination procedure that suffers most from a lack of standardization, despite the fact that it is a key determinant of the overall quality of reporting.

34.2.1 Colour-Coded Inking

Following formalin fixation, all relevant surfaces of pancreatoduodenectomy or distal pancreatectomy specimens are inked in a colour-coded fashion (Fig. 34.1). This allows accurate reporting of the R-status and a detailed account of the tumour site and the relationship of the tumour to the margins. Special attention should be paid to the correct inking of additional margins in specimens from extended surgical procedures, which may include a venous or arterial resection, the left adrenal gland, left kidney, and/or part of the stomach, small bowel, or colon.

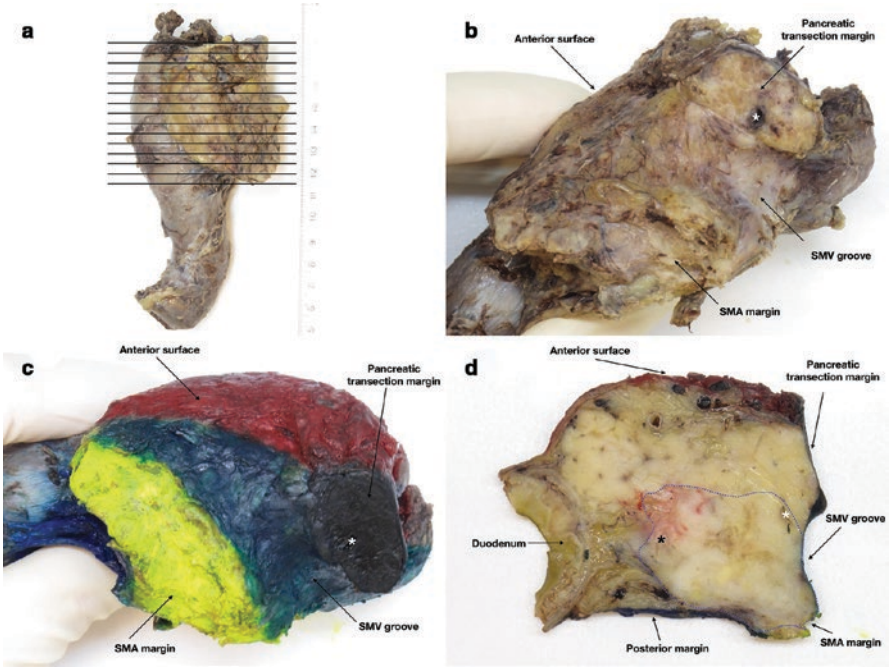

Fig. 34.1 Colour-coded inking and axial slicing of pancreatoduodenectomy specimens. Slicing in the axial plane, that is, perpendicular to the longitudinal axis of the descending duodenum, results on average in 12–15 axial specimen slices measuring 3–4 mm in thickness (**a**). Orientation of the specimen starts with the identification of the pancreatic transection margin and the smooth and slightly curved SMV-groove. The SMA-margin lies to the left of the latter and has a rough surface. Note the dilated main pancreatic duct (*asterisk*, **b**). Following specimen fixation, the various surfaces are inked in different colours: anterior surface (red), pancreatic transection margin (black), SMV-groove (green), SMA-margin (yellow). The specimen lies on the posterior surface (**c**). An axial specimen slice reveals a large ductal adenocarcinoma in the posterior-medial quadrant of the pancreatic head. Note that both the main pancreatic duct (*white asterisk*) and common bile duct (*black asterisk*) are obliterated by tumour (tumour periphery, *blue dotted line*) (**d**)

34.2.2 Specimen Dissection

Following formalin fixation and colour-coded inking, the specimen is dissected. Photodocumentation of the specimen slices is highly recommended, as it facilitates microscopic assessment, case review, and multidisciplinary discussion.

Given the complexity of the local anatomy, dissection of pancreatoduodenectomy specimens is more demanding than that of distal pancreatectomy specimens. Two different approaches are commonly used for dissection of the former. According to the so-called *bivalving technique*, the specimen is sliced along the plane defined by a probe in both the pancreatic duct and common bile duct, following which both halves are further sliced in another plane. Probing of the narrow, curved ducts is difficult, especially as they are often obstructed by tumour. By slicing in the plane of the ducts, the ampullary region is displayed in a longitudinal fashion, which may be helpful in cases with primary ampullary cancer. However, the display of the tissues away from the ampulla is either limited ("hidden" in the two thick halves of the pancreatic head) or fragmented, and given the different planes of dissection, it may be difficult to reconstruct the tumour in three dimensions, potentially compromising accurate assessment of tumour size and T-stage.

The second commonly used dissection technique is based on serial slicing in the axial plane (Fig. 34.1). *Axial slicing* is easy to perform, as every specimen is handled in exactly the same manner, and there is no need for probing of the pancreatic and/or bile duct. Furthermore, in case of an extended resection, the vascular resection can be sliced *en bloc* with the pancreas, following the same simple axial slicing protocol. As the plane of slicing is always the same, reconstruction of the tumour in a mental 3-dimensional image is straightforward, which is key to correct measurement of the tumour size and attribution of pT-stage and R-status [11]. Because the axial dissection plane is the same as the one used in CT and MRI scanning, the tumour and surrounding local anatomy are displayed in the same way in both axial specimen slices and CT/MRI images, which greatly facilitates correlation between pathology findings and preoperative imaging.

Specimen dissection and subsequent macroscopic examination of the specimen slices is of particular importance for the correct identification of the cancer origin, that is, for the distinction between cancer arising from the pancreas, ampulla of Vater, common bile duct, or duodenum. Because there are no reliable microscopic criteria to distinguish these entities, the location of the centre of the tumour mass is decisive for the identification of the cancer origin [9]. In large tumours that involve multiple structures, this may occasionally be difficult.

Distal pancreatectomy specimens are dissected by serial slicing in the sagittal plane, which is usually straightforward and can be applied also to extended surgical specimens that include, for example, the left adrenal gland (Fig. 34.2).

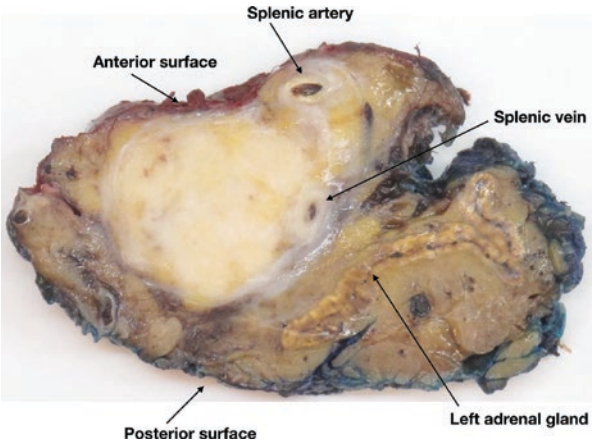

Fig. 34.2 Extended distal pancreatectomy specimen. This specimen slice shows a large ductal adenocarcinoma, which involves almost the entire width of the pancreatic body and extends into the peripancreatic fat, both anteriorly close to the inked surface (red) and posteriorly with involvement of the splenic vein. The adrenal gland is clear of tumour

34.2.3 Tissue Sampling

There are no guidelines regarding the method and extent of tissue sampling, despite the fact that both are critical determinants of the quality of pathology reporting. Limited sampling may lead to underestimation of tumour size and margin involvement. Ductal adenocarcinoma is notoriously poorly circumscribed, due to the highly dispersed growth pattern, which results in the presence of invasive cancer cell clusters well beyond the macroscopic tumour bed (Fig. 34.3). This means that the *periphery* of the grossly visible tumour should be sampled preferentially, including the adjoining, seemingly tumour-free tissues, in order to capture the full (microscopic) tumour extent. Extensive en-bloc sampling of the tumour onto the peripancreatic tissues and specimen surface ensures the identification of microscopic, that is, macroscopically imperceptible margin involvement (R1). At the same time it is key to achieving an adequate lymph node yield. Extensive tissue sampling is particularly important for tumours that have been treated neoadjuvantly, because the tumour boundaries are additionally obscured by treatment-induced fibrotic changes. In practice, this means that most of the pancreas and relevant adjacent tissues have to be sampled.

'Orange peeling' is an alternative way of lymph node sampling, typically undertaken prior to bivalving of a pancreatoduodenectomy specimen. With this approach, the peripancreatic adipose tissue is shaved from the pancreatic head and completely embedded [12]. While this technique aims at increasing the lymph node yield, it disrupts the relationship of the tumour to the peripancreatic fat and margins, hence compromising measurement of the tumour size and microscopic assessment of the R-status.

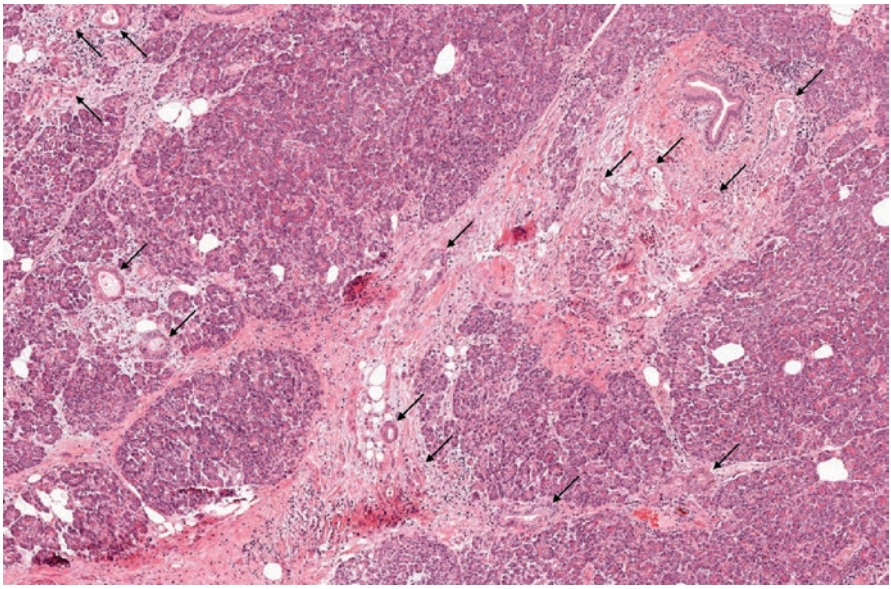

Fig. 34.3 Dispersed growth pattern of ductal adenocarcinoma. Tumour glands of a well-differentiated ductal adenocarcinoma (*arrows*) infiltrate nonneoplastic pancreatic parenchyma without causing distortion or fibrosis of pre-existing tissues, that is, without being macroscopically visible. This phenomenon, often observed in the tumour periphery, commonly leads to significant underestimation of both the tumour size and extent based on macroscopic examination

34.3 Microscopic Examination

34.3.1 Pancreatic Ductal Adenocarcinoma and Subtypes

In ductal adenocarcinoma, tumour glands are characteristically surrounded by a large amount of desmoplastic stroma, which consists of abundant extracellular matrix and pancreatic stellate cells or so-called cancer-associated fibroblasts. Consequently, cancer cells account for about only a third, and occasionally as little as 5% of the total tumour volume. This low cancer cell density may reduce the chance of obtaining a representative fine needle biopsy. Furthermore, it is an obstacle to bulk molecular analysis of tumour tissue samples, as the signal from the cancer cells may be significantly diluted by that of other "contaminating" cell populations, first and foremost pancreatic stellate cells and inflammatory cells.

The WHO classification defines a number of subtypes of pancreatic ductal adenocarcinoma that have distinct morphological features and differ molecularly and in clinical outcome from the common form of ductal adenocarcinoma, also called ductal adenocarcinoma *not otherwise specified (NOS)* [1]. These subtypes are rare and account for <5% of all ductal adenocarcinomas. *Colloid carcinoma* consists predominantly of tumour cells that show intestinal differentiation and are suspended in

large extracellular mucin pools. While typically of large size, colloid carcinoma is associated with a better prognosis. *Adenosquamous carcinoma* shows squamous differentiation in ≥30% of the tumour mass and has a particularly poor prognosis. *Medullary carcinoma* of the pancreas is exceedingly rare and characterized by high cellularity, poor differentiation, and prominent lymphocytic infiltration. This subtype is strongly associated with mismatch repair deficiency and may occur sporadically or in the setting of Lynch syndrome.

While ductal adenocarcinoma NOS is defined by the WHO as having no specific histological features, recent studies indicate that a wide range of morphological variation exists within this large tumour group. This morphological heterogeneity, which occurs both within the same tumour and between patients, is not described in the WHO classification, and consequently, the prevalence and clinical relevance of it are currently unknown [13]. Recent evidence suggests that morphological variation is indeed linked with differences at the genomic and transcriptome level [14, 15].

34.3.2 TN-staging

The defining criteria of *T-stage* in pancreatic cancer were recently changed [2, 3]. Stages T1-T3 are now exclusively determined by tumour size (<2 cm, 2–4 cm, >4 cm, respectively), irrespective of the presence or absence of extrapancreatic tumour extension, while stage T4 has remained unaltered and is defined by involvement of the superior mesenteric artery, coeliac trunk, or common hepatic artery (see Chap. 14). As outlined above, accurate measurement of tumour size, both macroscopically and microscopically, is not without its difficulties. Indeed, given the dispersed tumour growth and presence of pronounced fibrosis, accurate measurement of tumour size can only be done microscopically, but this requires 3D-reconstruction of the tumour across multiple specimen slices. While interobserver agreement in tumour size assessment is obviously of key importance for the reliability of T-staging, it has not been assessed but is suspected to be suboptimal.

The *N-stage* reflects the extent of regional lymph node metastasis and is subdivided in N1 (1–3 positive lymph nodes) and N2 (≥4 lymph node metastases). Nearly 80% of patients with ductal adenocarcinoma have at least one positive lymph node [16]. Recording of the total lymph node yield is compulsory, as the prognostic relevance of the N-status is dependent on the examination of an adequate number of lymph nodes. In pancreatoduodenectomy specimens, ≥12 lymph nodes are required for reliable staging of node-negative tumours [17, 18]. For distal pancreatic resections the lymph node yield is typically lower, but there is no defined minimum yield [19]. Similarly, fewer lymph nodes are usually found in specimens with neoadjuvantly treated ductal adenocarcinoma, but the impact of the lymph node yield on the prognostic relevance of N-staging has not been investigated in this setting.

34.3.3 Additional Descriptors

Tumour *propagation along lymphatics and blood vessels*—reported as L1 and V1, respectively—is part of the minimum data set of pathology reporting, although the prognostic impact of both descriptors is smaller than that of T- and N-stage. Especially in cases with lymph node metastasis, the L-status is obviously of no additional clinical information. Tumour *propagation along perineurial clefts*—recorded as Pn1—results in locoregional and extraregional tumour spread and is associated with shorter tumour-free and overall survival [20]. While perineural invasion is exceedingly common and recorded in nearly all resected ductal adenocarcinomas, its extent may vary significantly between individual cases [21]. Unfortunately, with the current binary recording system—Pn0 or Pn1—quantitative information is not provided, which probably limits the prognostic value of this feature.

The *grade of differentiation* of ductal adenocarcinoma reflects to some extent the intrinsic aggressiveness of the tumour. It is based on the degree of gland formation and cytological pleomorphism, while mucin production and mitotic activity may also be taken into consideration [22]. Low differentiation is generally associated with poorer prognosis [23, 24]. Because the grade of differentiation often varies within a tumour, assessment of this data item suffers from interobserver variation.

34.3.4 Margin Assessment and R-status

For pancreatoduodenectomy specimens the following surfaces should be included in the assessment of the margins: (1) the transection margins of the pancreatic neck, common bile duct, and stomach/duodenum, (2) the bluntly dissected margins, that is, the posterior surface and groove of the superior mesenteric vein (SMV)/portal vein, (3) the sharply dissected margin towards the superior mesenteric artery, and (4) the anterior surface, which is peritonealized and faces the lesser sac. In distal pancreatectomy specimens, the pancreatic transection margin, the transection margin of the splenic artery and vein, the posterior margin, and the anterior surface should be examined. In extended resection specimens, the surfaces of the additionally resected structures should be included in the margin assessment.

Some confusion exists as to whether the anterior surface should be taken into account for the R-status, given that it is not a surgical margin. However, considering that “R” stands for *residual disease* rather than resection margin, the status of the anterior surface should be reported. Indeed, breaching of the anterior surface by tumour cells portends the risk of residual disease and local tumour recurrence [25].

In most countries, the presence of tumour cells <1 mm from a surgical transection or dissection margin is considered R1. This definition excludes the anterior free surface: here the tumour cells should breach the surface (0 mm clearance) for the diagnosis of R1. The 1 mm definition is supported by multiple studies, which have shown that an R0 resection only carries prognostic value when it is defined as

≥1 mm margin clearance. In the majority of patients (80%), resection is microscopically incomplete (R1). Adequate sampling is of key importance for the assessment of R-status, as the R1 rate increases with the number of tissue blocks that are taken from the tumour onto the overlying surfaces [26, 27]. Interestingly, in cases with involvement of the SMV, venous resection does not usually result in an R0 resection. The reason is twofold: (1) microscopic margin involvement is often still present at the SMV margin around the resected vein and, (2) in a large proportion of cases, margin involvement is multifocal, that is, margins other than the SMV surface are positive [28].

34.4 Neoadjuvant Treatment

Pathology examination of pancreatic cancer specimens following neoadjuvant treatment can be challenging, because tumour regression is often patchy, and macroscopically, it is often impossible to distinguish areas with residual cancer from those with fibrosis devoid of viable cancer cells (Fig. 34.4) [29]. Consequently, extensive tissue sampling is essential for accurate assessment of the residual cancer. There is no guidance on how to measure the tumour size if the residual cancer is present in

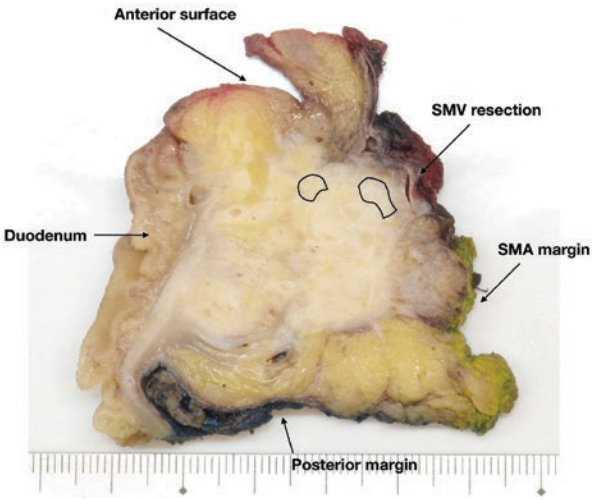

Fig. 34.4 Pancreatoduodenectomy specimen with venous resection following neoadjuvant treatment of a borderline resectable ductal adenocarcinoma. An axial specimen slice shows extensive and ill-circumscribed abnormal white tissue, which involves most of the pancreatic parenchyma and extends into the peripancreatic fat anteriorly, towards the irregular SMA-margin, and towards the segment of SMV. Note the thickened wall and stenosed lumen of the latter. Based on microscopic examination, viable cancer cells were found in only two small foci (*black line*), which are macroscopically indistinguishable from extensive areas of fibrosis

two or more separate foci, which is often the case. Currently, there are two approaches: (1) measurement along a line that connects the tumour foci that are furthest away from each other (i.e., including intervening non-neoplastic tissue), and (2) summation of the size of individual foci (i.e., excluding intervening non-neoplastic tissue). In some cases, both approaches may give significantly different results, and consequently, assignment to different T-stages.

Assessment of the effect of neoadjuvant treatment is based on an estimation of either the decrease in tumour cells (i.e. tumour regression grading) or the quantity of residual cancer. Regression grading is problematic because the extent and cellularity of the cancer *before* treatment are unknown, hence the relative change in either cannot be assessed [30]. Compounding this problem, the response to treatment often varies considerably within the tumour, making it difficult to represent this variegated result with a single score.

Given these fundamental difficulties and considering the rapidly increasing use of neoadjuvant treatment in clinical practice, international efforts are currently being undertaken to improve and standardize the pathology reporting of these challenging specimens.

34.5 Preoperative Diagnostics

As explained above, due to the dispersed growth of pancreatic cancer, fine needle aspirates and biopsies often contain only a small number of lesional cells, such that a confident diagnosis may be difficult to make. Distinguishing ductal adenocarcinoma from reactive ductular structures may be challenging, and immunohistochemical investigation is often of limited if any help. In case a diagnosis of adenocarcinoma can be established, distinction between primary pancreatic and for example duodenal cancer may be impossible, especially because pancreatic cancer may show intestinal mimicry, that is, adopt a more intestinal morphology as it infiltrates the duodenal wall. As there is no specific immunohistochemical signature for ductal adenocarcinoma, distinction from adenocarcinoma of extrapancreatic (in particular upper gastrointestinal) origin may be difficult [31, 32].

References

1. Lokuhetty D, White V, Watanabe R, Cree IA, editors. Digestive system tumours. WHO classification of tumours. 5th ed. Lyon: IARC Press; 2019.
2. Brierly JD, Gospodarowicz MK, Wittekind C, editors. UICC TNM classification of malignant tumours. 8th ed. London: Wiley-Blackwell; 2016.
3. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jesus JM, Brierley JD, Gaspard LE, Shcilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR (eds) (2017). AJCC cancer staging manual, 8, Springer, New York, NY.

4. Kakar S, Shi C, Adsay NV, Fitzgibbons P, Frankel WL, Klistra DS, Karsinskas AM, Mino-Kenudson M, Pawlik T, Vauthey J-N, Washington MK. Protocol for the examination of specimens from patients with carcinoma of the pancreas. Northfield, IL: College of American Pathologists (CAP); 2017.
5. Campbell F, Cairns A, Duthie F, Feakins R. Dataset for the histopathological reporting of carcinoma of the pancreas, ampulla of Vater and common bile duct. 2017. www.rcpath.org. Accessed 30 Dec 2019.
6. The Royal College of Pathologists of Australasia. Cancer of the exocrine pancreas, ampulla of Vater and distal common bile duct. Structured reporting protocol. 2014. https://www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols. Accessed 30 Dec 2019.
7. ICCR (International Collaboration on Cancer Reporting). Carcinoma of the exocrine pancreas. Histopathology Reporting Guide. 2020. http://www.iccr-cancer.org/datasets/published-datasets/digestive-tract.
8. Feakins R, Campbell F, Verbeke CS. Survey of UK histopathologists' approach to the reporting of resection specimens for carcinomas of the pancreatic head. J Clin Pathol. 2013;66:715–7.
9. Verbeke CS, Gladhaug IP. Resection margins involvement and tumour origin in pancreatic head cancer. Br J Surg. 2012;99:1036–49.
10. Soer E, Brosens L, van de Vijver M, Dijk F, van Velthuysen ML, FarinaSarasqueta A, Morreau H, Offerhaus J, Koens L, Verheij J. Dilemmas for the pathologist in the oncologic assessment of pancreatoduodenectomy specimens: an overview of different grossing approaches and the relevance of the histopathological characteristics in the oncologic assessment of pancreatoduodenectomy specimens. Virchows Arch. 2018;472:533–43.
11. Chandrasegaram MD, Goldstein D, Simes J, Gebski V, Kench JG, Gill AJ, Samra JS, Merrett ND, Richardson AJ, Barbour AP. Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. Br J Surg. 2015;102:1459–72.
12. Adsay NV, Basturk O, Saka B, Bagci P, Ozdemir D, Balci S, Sarmiento JM, Kooby DA, Staley C, Maithel SK, Everett R, Cheng JD, Thirabanjasak D, Weaver DW. Whipple made simple for surgical pathologists: orientation, dissection, and sampling of pancreaticoduodenectomy specimens for a more practical and accurate evaluation of pancreatic, distal common bile duct, and ampullary tumors. Am J Surg Pathol. 2014;38:480–93.
13. Verbeke C. Morphological heterogeneity in ductal adenocarcinoma of the pancreas - does it matter? Pancreatology. 2016;16:295–301.
14. Schlitter AM, Segler A, Steiger K, Michalski CW, Jäger C, Konukiewitz B, Pfarr N, Endris V, Bettstetter M, Kong B, Regel I, Kleeff J, Klöppel G, Esposito I. Molecular, morphological and survival analysis of 177 resected pancreatic ductal adenocarcinomas (PDACs): identification of prognostic subtypes. Sci Rep. 2017;7:41064.
15. Kalimuthu SN, Wilson GW, Grant RC, Seto M, O'Kane G, Vajpeyi R, Notta F, Gallinger S, Chetty R. Morphological classification of pancreatic ductal adenocarcinoma that predicts molecular subtypes and correlates with clinical outcome. Gut. 2020;69:37. https://doi.org/10.1136/gutjnl-2019-318217.
16. van Roessel S, Strijker M, Steyerberg EW, Groen JV, Mieog JS, et al. International validation and update of the Amsterdam model for prediction of survival after pancreatoduodenectomy for pancreatic cancer. Eur J Surg Oncol. 2020;46:796. https://doi.org/10.1016/j.ejso.2019.12.023.
17. Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol. 2008;15:165–74.
18. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large U population database. Ann Surg Oncol. 2006;13:1189–200.
19. Sahakyan MA, Haugvik SP, Røsok BI, Kazaryan AM, Ignajatovic D, Buanes T, Labori KJ, Verbeke CS, Edwin B. Can standardized pathology examination increase the lymph

node yield following laparoscopic distal pancreatectomy for ductal adenocarcinoma? HPB. 2018;20:175–81.
20. Schorn S, Demir IR, Haller B, Scheufele F, Reyes CM, Tieftrunk E, Sargst M, Goess R, Friess H, Ceyhan GO. The influence of neural invasion on survival and tumor recurrence in pancreatic ductal adenocarcinoma - a systematic review and meta-analysis. Surg Oncol. 2017;26:105–15.
21. Liebl F, Demir IE, Mayer K, Schuster T, D'Haese JG, Becker K, Langer R, Bergmann F, Wang K, Rosenberg R, Novotny AR, Feith M, Reim D, Friess H, Ceyhan GO. The impact of neural invasion severity in gastrointestinal malignancies. A clinicopathological study. Ann Surg. 2014;260:900–8.
22. Klöppel G, Lingenthal G, von Bülow M, Kern HF. Histological and fine structural features of pancreatic ductal adenocarcinomas in relation to growth and prognosis: studies in xenografts tumours and clinic-histopathological correlation in a series of 75 cases. Histopathology. 1985;9:841–56.
23. Wasif N, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? Ann Surg Oncol. 2010;17:2312–20.
24. Rochefort MM, Ankeny JS, Kadera BE, Donald GW, Isacoff W, Wainberg ZA, Hines OJ, Donahue TR, Reber HA, Tomlinson JS. Impact of tumor grade on pancreatic cancer prognosis: validation of a novel TNMG staging system. Ann Surg Oncol. 2013;20:4322–9.
25. Nagakawa T, Sanada H, Inagaki M, Sugama J, Ueno K, Konishi I, Ohta T, Kayahara M, Kitagawa H. Long-term survivors after resection of carcinoma of the head of the pancreas: significance of histologically curative resection. J Hepato-Biliary-Pancreat Surg. 2004;11:402–8.
26. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. Br J Surg. 2006;93:1232–7.
27. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, Schuhmacher P, Büchler MW. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008;15:1651–60.
28. Kleive D, Labori KJ, Line PD, Gladhaug IP, Verbeke CS. Pancreatoduodenectomy with venous resection for ductal adenocarcinoma rarely achieves complete (R0) resection. HPB (Oxford). 2020;22:50. https://doi.org/10.1016/j.hpb.2019.05.005.
29. Verbeke C, Löhr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev. 2015;41:17–26.
30. Verbeke C, Häberle L, Lenggenhager D, Esposito I. Pathology assessment of pancreatic cancer following neoadjuvant treatment: time to move on. Pancreatology. 2018;10:467–76.
31. Bledsoe JR, Shinagare SA, Deshpande V. Difficult diagnostic problems in pancreatobiliary neoplasia. Arch Pathol Lab Med. 2015;139:848–57.
32. Xue Y, Vanoli A, Balci S, Reid MM, Saka B, Bagci P, et al. Non-ampullary duodenal carcinomas: clinicopathologic analysis of 47 cases and comparison with ampullary and pancreatic adenocarcinoma. Mod Pathol. 2017;30:255–66.

Chapter 35
Rare Tumors of the Pancreas

Lena Haeberle, Andrea Cacciato Insilla, and Irene Esposito

Take Home Messages

- Rare tumors of the pancreas include potentially malignant and malignant epithelial neoplasms as well as benign, potentially malignant, and malignant non-epithelial neoplasms of the pancreas.
- In addition, intrapancreatic metastases as well as tumor-like lesion of the pancreas, e.g. in the context of malformation or inflammation, should be taken into consideration when establishing a diagnosis.
- Close interdisciplinary cooperation is needed to ensure correct diagnosis and adequate management of rare tumors of the pancreas.

Pearls and Pitfalls

- Many rare tumors of the pancreas show distinct morphological features, immunophenotypes, and molecular signatures. However, unusual presentations and overlapping features exist, especially in rare epithelial neoplasms, and may hamper initial diagnosis.
- For example, solid-pseudopapillary neoplasms may express cytokeratins and neuroendocrine markers, and must be distinguished from neuroendocrine tumors (NETs) by their nuclear expression of beta-Catenin and/or molecular detection of CTNNB1 mutation. Similarly, acinar cell carci-

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noma and pancreatoblastoma can be distinguished from NET by their expression of Trypsin. In some cases, demographic factors can aid in distinguishing between entities, e.g. in the distinction between pancreatoblastoma, which is practically only observed in children, and acinar cell carcinoma, which is much more common in adult patients.
- In general, combining all available clinical, radiological, and pathological information is the best approach to reach a correct diagnosis.

Future Perspectives
- Data on rare tumors of the pancreas are still limited. With continuous improvements of imaging techniques, the number of diagnosed rare pancreatic tumors is rising, leading to an increase of available data. At the same time, techniques for molecular profiling, e.g. next generation sequencing, are being further refined and becoming more readily available, resulting in additional options to detect characteristic molecular signatures. This will increase the number of cases where a specific diagnosis can be made even though only scarce diagnostic material, e.g. small biopsies or cyst fluids, are available.

35.1 Introduction

Rare disorders are defined in Europe as diseases occurring with a prevalence of less than 50 cases out of a population of 100,000 [1]. According to this definition, most pancreatic tumors, including variants of pancreatic ductal adenocarcinoma, belong to the category of rare diseases. With the exception of high-volume referral centers, it is therefore unlikely for physicians to be confronted with these entities during their professional life. However, apart from ductal adenocarcinoma, a number of other rare tumors and tumor-like lesions may occur in the pancreas, therefore representing a diagnostic and therapeutic challenge. These rare tumors/tumor-like lesions can be classified in epithelial and non-epithelial as well as in benign and (potentially to certainly) malignant (Table 35.1). In the following sections, the main morphological characteristics of rare pancreatic tumors and tumor-like lesions and their clinical manifestations are described. Pancreatic metastases are not considered in this chapter.

Table 35.1 Rare tumors of the pancreas

Rare epithelial neoplasms		
	Entity	*Subtype/variant*
Potentially malignant	Solid pseudopapillary neoplasm (SPN)	
Malignant	Acinar cell carcinoma (ACC)	Acinar cell cyst adenocarcinoma
	Pancreatoblastoma	
Rare non-epithelial neoplasms		
Benign	Haemangioma	
	Lymphangioma	
Potentially malignant	PEComa	Angiomyolipoma
	Teratoma	Solid teratoma Cystic teratoma
	Gastrointestinal stroma tumor (GIST)	
	Solitary fibrous tumor (SFT)	
Malignant	Sarcomas	Leiomyosarcoma Rhabdomyosarcoma Liposarcoma Haemangioendothelioma Undifferentiated pleomorphic sarcoma

35.2 Rare Epithelial Neoplasms of the Pancreas

35.2.1 Potentially Malignant

35.2.1.1 Solid Pseudopapillary Neoplasm (SPN)

SPN of the pancreas is a low grade malignant neoplasm, accounting for less than 3% of all primary pancreatic tumors, and about 5% of all pancreatic cystic tumors [2, 3]. They occur predominantly in young women, usually in the second and third decade, while affected males are slightly older (mean age 35 years vs. 28 years) [4–6]. SPNs usually appear as single, large, and well-demarcated tumors, with a mean size of about 8–10 cm, and a diameter that may exceed 20 cm [5]. Cut surface shows a combination of solid and pseudocystic spaces and usually extensive necrotic and/or hemorrhagic areas (Fig. 35.1a) [4]. Microscopically, they are characterized by fibrovascular stalks lined by poorly cohesive cells containing

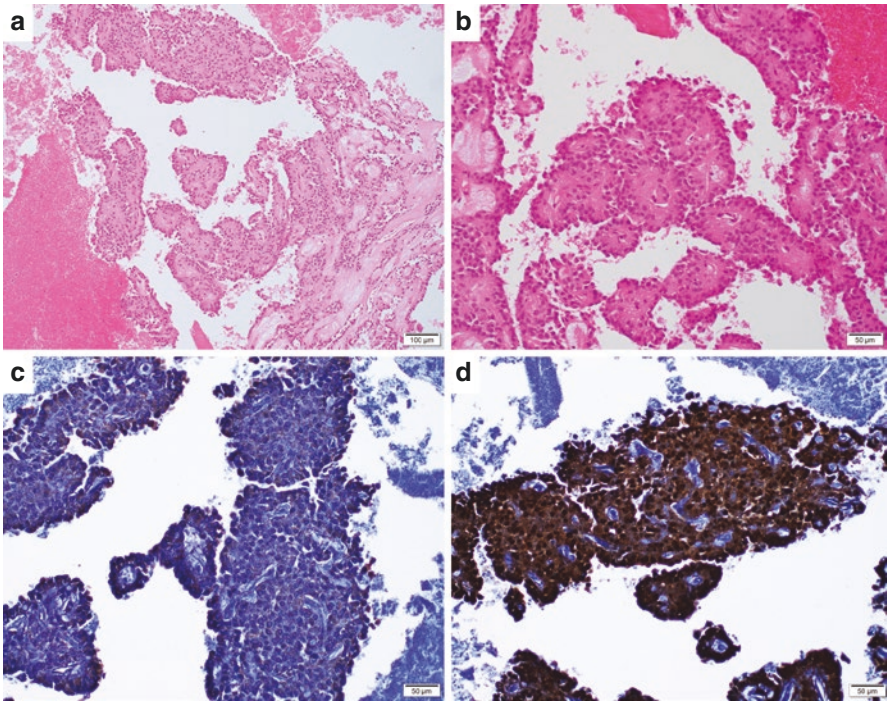

Fig. 35.1 Solid pseudopapillary neoplasm. (**a**) Solid pseudopapillary neoplasm displaying solid and pseudocystic areas with hemorrhages (HE, 100×). (**b**) On higher magnification, pseudopapillary projections lined by monomorphous cells can be seen (HE, 200×). The lesion stains positive for Vimentin (**c**, 200×) and shows nuclear positivity for beta-Catenin in immunohistochemistry (**d**, 200×)

PAS-positive globules, and characteristic grooved nuclei; mitotic figures are uncommon (Fig. 35.1b) [5]. Tumor cells usually express nuclear beta-Catenin, CD10, Vimentin, and alpha1-Antitrypsin (Fig. 35.1c, d); cytokeratins are detected in about 30% of cases; focal positivity for Synaptophysin and rarely for Chromogranin A has been reported [7]. SPNs generally present with excellent prognosis [2, 7, 8]. Malignancy is reported in up to 15% of cases, and 10–15% of patients develops metastasis, often in the liver and peritoneum [4–6]. Given the excellent prognosis, surgery with sparing of as much pancreatic tissue as possible is considered the optimal treatment, even in presence of distant metastases or local invasive effects [4]. Late recurrence pattern has been reported and most relapses occurred more than 5 years after resection, so a >5-year follow up is necessary after surgery [2, 9].

35.2.2 Malignant

35.2.2.1 Pancreatoblastoma

Pancreatoblastoma is a very rare malignant neoplasm. Nevertheless, it represents the most common pancreatic tumor in children, accounting for about 25% of all pancreatic neoplasms before 10 years of age [10]. Some adult cases have been reported, with a slight predominance in males and a median age of 37 years (range 18–78 years) [11–13]. Most cases are sporadic, but association with genetic syndromes, such as the Beckwith–Wiedemann syndrome or the familial adenomatous polyposis syndrome has been described [14, 15]. The presenting features of pancreatoblastoma are not specific and many cases are discovered incidentally [10, 16]. Cases characterized by inappropriate secretion of antidiuretic hormone or ACTH have been reported, leading to development of endocrine syndromes [10]. Serum AFP is a common serological marker, that does not correlate with tumor size, although its normalization is often observed after effective therapies. Elevated levels of CEA and CA19.9 might be also present, especially in children [10, 17, 18].

Pancreatoblastoma typically presents as a large, solid and well-demarcated neoplasm, tan to whitish on cut surface, with possible features of cystic degeneration and hemorrhagic necrosis. Histologically, it is composed of highly cellular lobules separated by fibrous bands, with occasional occurrence of heterologous elements. The neoplastic cells resemble those found in acinar carcinomas (Fig. 35.2a, b); however, other cell types can be observed, including neuroendocrine or ductal elements. Presence of squamoid nests is considered a characteristic feature (Fig. 35.2c, d), critical for the diagnosis, but the distribution of this component is often not uniform, hence not always identifiable in small biopsies. Mitotic figures might be frequent and vascular and perineural invasion can also occur [11, 18, 19].

Pancreatoblastomas exhibit a malignant behavior and are less aggressive in children than in adults [13, 20]. Metastases are present in up to 35% of cases, with regional lymph nodes, liver, lung and brain as most common metastatic sites [10, 13].

Complete surgical excision still represents the most important prognostic factor, associated with a 5-year survival rate of 65% in localized disease; patients with unresectable disease have a poorer prognosis and a survival usually shorter than 5 years [10, 16].

35.2.2.2 Acinar Cell Carcinoma

Acinar cell carcinoma (ACCs) is a malignant epithelial neoplasm of the pancreas with acinar cell differentiation [21], i.e. morphological resemblance of acinar cells and the production of exocrine enzymes. ACCs are very rare, accounting for only

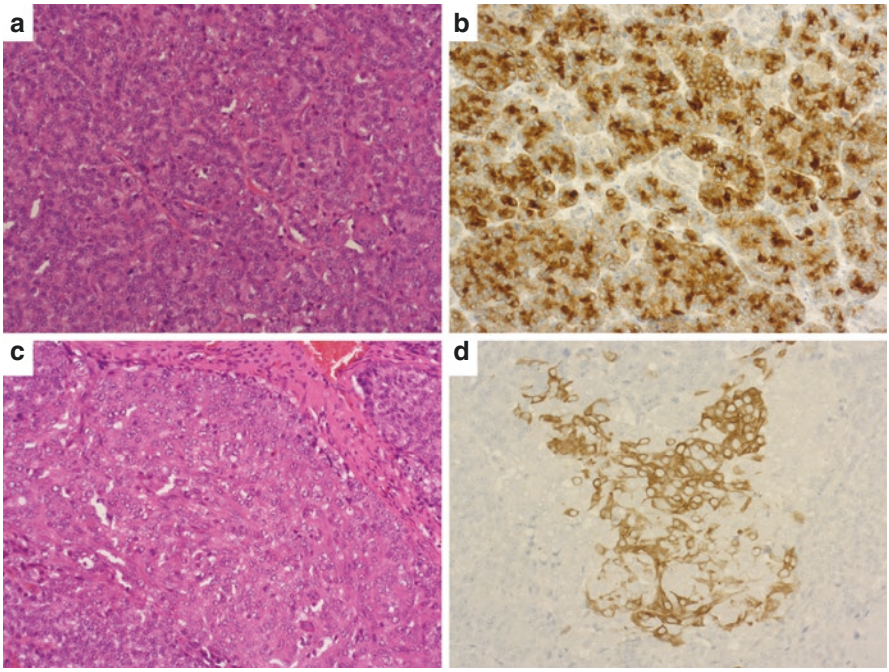

Fig. 35.2 Pancreatoblastoma. (**a**) Pancreatoblastoma with a diffuse, partly acinar-like growth pattern, consisting of tumor cells with slim amphiphilic cytoplasm and round, relatively monomorphic nuclei (HE, 200×). (**b**) These tumor cells stain positive for Trypsin (200×). (**c**) In addition, a second tumor cell component with nodular growth and larger tumor cells with wide eosinophilic cytoplasm and equally round and monomorphic nuclei can be appreciated (HE, 200×). (**d**) The cells of the second tumor cell component stain positive for CK5 (200×)

1–2% of pancreatic neoplasms, show a male predominance, and are mostly diagnosed in adults with a mean age at diagnosis of approximately 60 years, although they may also present in children [22]. Symptoms of patients with ACC are usually unspecific, including abdominal pain, nausea and vomiting, and weight loss, although in rare cases, symptoms related to elevated serum lipase levels (polyarthralgia and fat necrosis of subcutaneous tissue) may occur [22]. Elevated serum levels of AFP have been reported in ACC patients, albeit very rarely [23].

ACCs can arise in any portion of the pancreas. Macroscopically, ACCs are usually well-circumscribed, large (average diameter 8–10 cm), solid tumors with a soft, "fleshy" cut surface, which may show hemorrhage and/or necrosis [22]. Histologically, they may show a lobular growth pattern and form clusters or nests with small lumina recapitulating the architecture of acini of the normal pancreas (Fig. 35.3a), but they may also display a solid sheet-like, glandular, trabecular or other growth pattern [22]. The tumor cells are characterized by a slightly eosinophilic cytoplasm containing PAS-positive zymogene granules (Fig. 35.3b), and typically show enlarged nuclei,

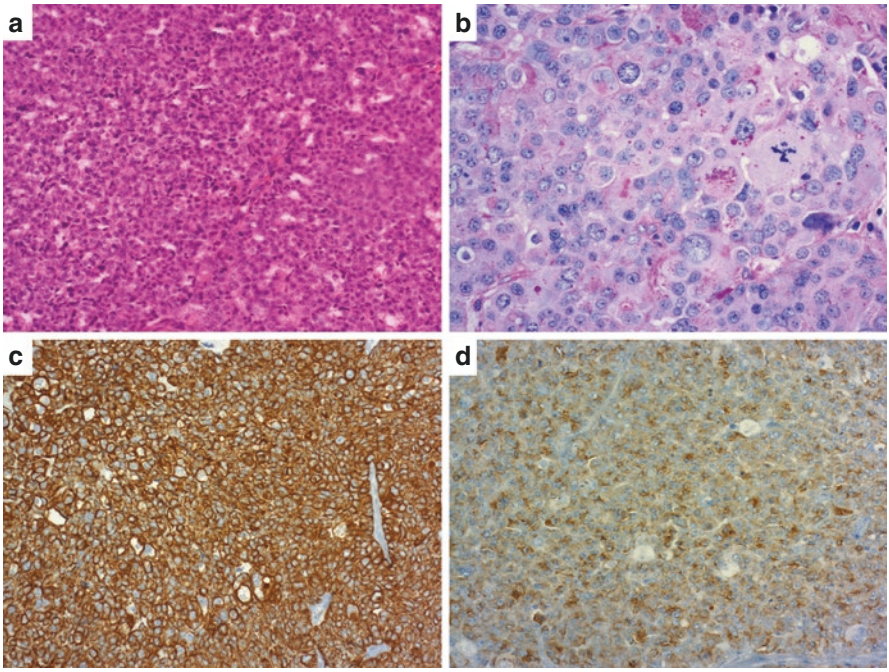

Fig. 35.3 Acinar cell carcinoma. (**a**) Acinar cell carcinoma showing a solid-acinar growth pattern with dense cell clusters forming minute lumina (HE, 200×). (**b**) PAS-positive granules are the histomorphological correlate for zymogens produced by the tumor cells (PAS, 400×). (**c**) Tumor cells stain positive for CK8 in immunohistochemistry (200×). (**d**) Additional positivity for Trypsin confirms the diagnosis of acinar cell carcinoma (200×)

which most commonly lack marked pleomorphism and can contain a characteristic single prominent nucleolus. In immunohistochemistry, ACCs stain positive for cytokeratins (Fig. 35.3c). The presence of pancreas enzymes, such as Trypsin, can also be confirmed by immunohistochemistry (Fig. 35.3d) [22].

ACCs show regional invasive growth as well as lymph node and distant metastasis, i.e. to the liver. The prognosis of ACC is poor, albeit slightly better than the prognosis of pancreatic ductal adenocarcinoma. For resected patients, the 5-year-survival rate is reported to be around 25% [24].

35.2.2.3 Acinar Cell Cystadenocarcinoma

Acinar cell cystadenocarcinoma is considered a subtype of acinar cell carcinoma [21], which is even rarer than conventional solid ACC. They are usually large multicystic lesions lined by epithelium resembling that of ACC and, other than their cystic nature, share all features of conventional ACC.

35.3 Rare Non-epithelial Neoplasms in of the Pancreas

35.3.1 Benign

35.3.1.1 Haemangioma

Hemangiomas occur very rarely in the pancreas and are more commonly reported during childhood, with only few cases in adults [25]. Pancreatic hemangiomas initially present with a proliferating phase in children, followed by a period of involution lasting few years, and eventual regression leaving a fibro-fatty tissue [25, 26]. In adults, these lesions may present as multiloculated, blood-filled cystic spaces, lined by flat endothelium without atypia; depending on the size of vascular spaces, they can be capillary or cavernous type. Immunohistochemical analysis shows positivity for ERG, CD31 and CD34, but not for D2-40. Surgical excision seems a reasonable strategy for large hemangiomas, especially in cases with uncontrolled symptoms [27].

35.3.1.2 Lymphangioma

Lymphangiomas are benign, slow-growing neoplasms showing lymphatic differentiation, usually resulting from congenital lymphatic malformations. Lymphangiomas can arise at all sites in the gastro-intestinal tract, but their occurrence in the pancreas is uncommon, accounting for less than 0.2% of all pancreatic cystic-appearing neoplasms. Lymphangiomas are most commonly found in young females (ratio 2:1), although all age groups can be affected (range 2–81, median age 43 years), and are more frequently reported in the pancreatic body or tail [28–30]. Lymphangiomas are generally large at diagnosis (average size 12 cm) [34]. They present as cystic-like spaces lined by single layers of flat endothelial cells, containing serous or chylous fluid. Immunohistochemistry shows positivity for all lymphatic and capillary endothelial markers, like D2-40 and CD31 [29, 30]. Differential diagnosis include pseudocysts, other congenital cysts, serous cystic neoplasms, and hemangiomas [28]. Some authors advocate the usefulness of endoscopic ultrasound in the preoperative workout, with analysis of cystic fluid by fine-needle aspiration for cytology and triglycerides determination [28, 30].

35.3.2 Potentially Malignant

35.3.2.1 PEComa

Perivascular epithelioid cell neoplasms (PEComas) are well-vascularized tumors composed of epithelioid or spindle cells showing clear to focally granular eosinophilic cytoplasm, which grow in a nested and alveolar pattern around blood vessels

[31, 32]. Angiomyolipomas represent a PEComa subtype that also contains adipocytes and thick-walled blood vessels. Pancreatic PEComas can arise in patients of any age (mean age 47.9 years), with a strong female gender predilection [31]. The characteristic immunohistochemical profile includes positive melanocytic markers, such as HMB-45 and Melan-A, and occasionally myogenic markers, like alpha-Smooth muscle actin and Desmin [31]. Prognosis of pancreatic PEComas is relatively good with most cases following a benign course; however, tumor recurrence after surgery and metastasis are reported [31, 33]. Worrisome features correlating with malignant behavior include size >5 cm, infiltrative growth, hypercellularity, high nuclear grade, high mitotic figures and necrosis [31].

35.3.2.2 Teratoma

Teratomas are neoplasms of germ cell origin arising from (misplaced) embryogenic tissue. Therefore, teratomas are usually found in the ovary or testis, but can arise anywhere along the path of germ cell migration, which is usually along the midline of the body. In the pancreas, teratomas are exceedingly rare, and to date, only about 30 cases are reported in literature [34].

Usually, teratomas predominantly consist of ectodermal components like squamous epithelium, skin appendages and sebaceous material, but they may contain tissue from all three germinal layers, i.e. ectoderm, endoderm and mesoderm. Teratomas can be cystic or solid.

Based on the presence or absence of immature components, they can be classified as mature (benign) or immature (malignant).

35.3.2.3 Gastrointestinal Stromal Tumor (GIST)

Pancreatic gastrointestinal stromal tumors (GISTs) are extremely rare, and they usually represent secondary involvement of the pancreas from primary gastric or duodenal GIST. To date, only 39 cases of pancreatic GISTs in 45 patients have been reported in the English literature from 2001 to 2016 [35]. Vague abdominal pain or discomfort, weight loss, and fatigue are the most common clinical presentations [36]. Histologically, both epithelioid and spindle cell components have been described with a slight association between spindle cell GIST and solid macroscopic appearance [35]. Characteristic expression of CD117 and DOG1 is reported, as well as activating mutations of either KIT (up to 75% of cases) or PDGFRA (in about 10% of cases) [35, 37]. Differential diagnosis include leiomyoma and leiomyosarcoma, schwannoma, inflammatory fibroid polyps, and fibromatosis; in addition, pancreatic GISTs may have overlapping radiological appearances with neuroendocrine tumors and cystic pancreatic lesions [36, 37]. High mitotic index is considered the main risk factor in pancreatic GISTs, which frequently behave more aggressively than same neoplasms occurring in different gastrointestinal sites [35].

35.3.2.4 Solitary Fibrous Tumor (SFT)

Pancreatic SFT is extremely rare and only few cases have been described [38, 39]. It usually presents as a well-circumscribed, solitary, whitish, firm and slow-growing mass, with a slight predominance in the head of the pancreas [38]. Histologically, it is composed of bland spindle cells randomly arranged in a dense collagenous stroma; a well-developed vascular network is frequently observed, with thin-walled, branching blood vessels (stag-horn) surrounded by neoplastic cells with a concentric growth pattern. Mitoses are usually absent [39, 40]. On immunohistochemistry, neoplastic cells show diffuse positivity for CD34, BCL-2, and CD99; focal positivity for S100 can be observed. Cytokeratin (AE1/AE3), EMA, Smooth muscle actin, Desmin, CD117 and DOG1 are typically negative [38, 39]. Although SFT owns the potential for malignant transformation, to date, no malignant lesions have been described arising in the pancreas.

35.3.3 Malignant

35.3.3.1 Sarcomas

Primary sarcomas of the pancreas are extremely rare, accounting for about 0.1% of all pancreatic malignancies. Sarcomas of the pancreas occur more frequently in younger patients, with main involvement of the head of the pancreas, followed by body and tail [41]. Among pancreatic sarcomas, leiomyosarcomas tend to occur more frequently; others reported entities are rhabdomyosarcomas, liposarcomas, haemangioendotheliomas, and undifferentiated pleomorphic sarcomas [42, 43]. Pancreatic sarcomas tend to grow rapidly and are associated to a poor prognosis; patient age, tumor size, presence of tumoral necrosis, and vascular invasion are considered main prognostic factors [44]. They typically present as large, often well-circumscribed lesions, including features of necrosis and hemorrhage. Histologic analysis shows pleomorphic spindle cells with large atypical nuclei and numerous mitoses (Fig. 35.4a, b) [45]. Differential diagnosis is based on histology and immunohistochemistry (Fig. 35.4c, d), and therefore diagnosis is often difficult before surgery [38]. The sarcomatoid variant of undifferentiated pancreatic adenocarcinoma represents a diagnostic challenge.

35.4 Rare Tumor-Like Lesions of the Pancreas

35.4.1 Acinar Cystic Transformation

Acinar cystic transformation, in the past also referred to as acinar cell cystadenoma, is now thought to be a non-neoplastic cystic lesion of the pancreas whose etiology is not entirely clear [21]. Acinar cell cyst transformation is characterized by cystic

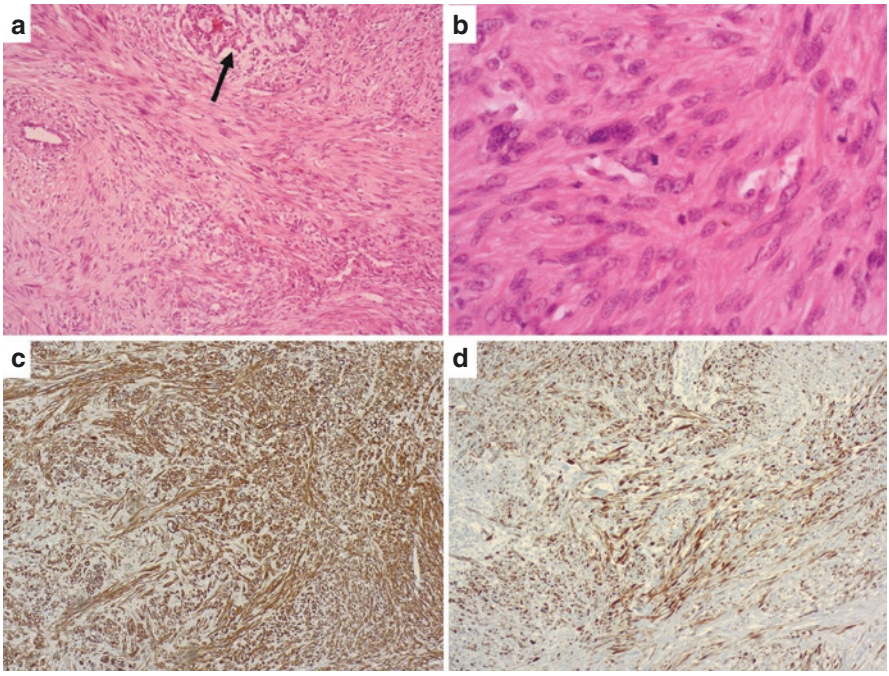

Fig. 35.4 Leiomyosarcoma of the pancreas. (**a**) Leiomyosarcoma of the pancreas presenting as spindle cell tumor with a fascicular growth pattern infiltrating the pancreas parenchyma (HE, 100×; arrow: remnant islet). (**b**) Higher magnification shows polymorphous hyperchromatic nuclei and mitotic figures (HE, 400×). The tumor is positive for Smooth muscle actin (c, 100×) and Desmin (**d**, 100×)

transformation, which usually affects part of the pancreas, but may also involve the entire organ diffusely or multifocally. Therefore, it can either appear as macroscopic lesion or be appreciated only incidentally upon microscopy. The lesion shows a predominance for female patients [46, 47]. In most cases, patients with acinar cystic transformation of the pancreas are asymptomatic, although in cases with large lesions, symptoms due to expansive growth, such as abdominal pain, may occur.

If grossly apparent, acinar cystic transformation presents as uni- or multilocular cystic lesion, usually with a thin, soft cyst wall without evidence of mucinous fluid or connection to the pancreatic duct system (Fig. 35.5a). Histologically, the cysts are lined by benign-appearing acinar and ductal epithelium (Fig. 35.5b, c), which can be confirmed by immunohistochemistry (i.e. for Trypsin and CK19) (Fig. 35.5d). Surrounding pancreatic parenchyma may be fibrotic and/or atrophic (Fig. 35.5b, c).

Although initially thought to be neoplastic, clonal studies on acinar cystic transformation were unable to support the neoplastic nature of the lesion [48], which is therefore considered non-neoplastic and may, at least in some cases, be a result of cystic dilation of ductulo-lobular units due to obstruction. To date, malignancy has never been reported in cases of acinar cystic transformation, resulting in an excellent prognosis.

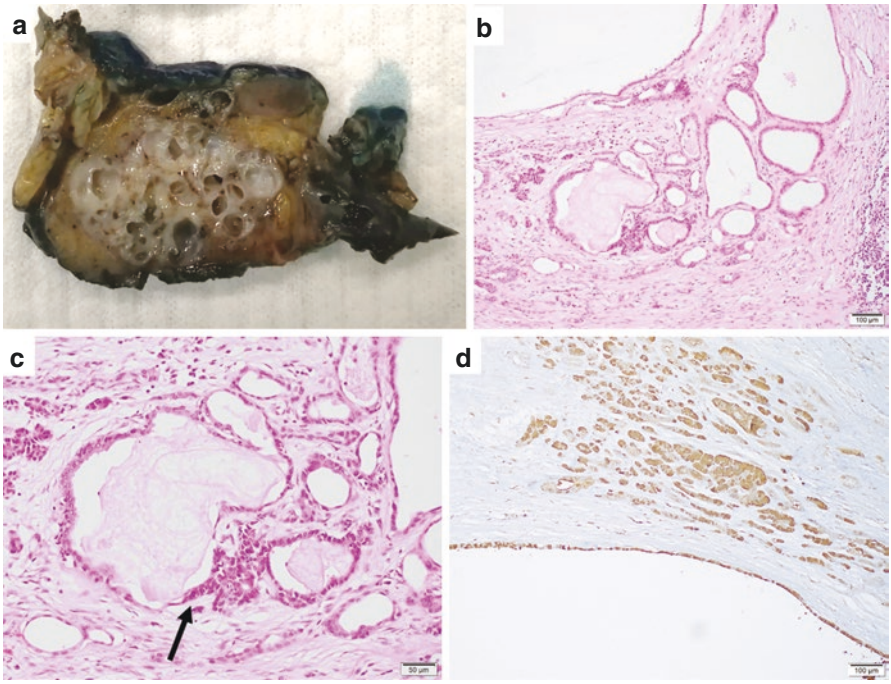

Fig. 35.5 Acinar cell cystic transformation. (**a**) Macroscopic image of acinar cell cystic transformation showing a multicystic lesion with smooth cyst walls and serous cyst fluid. (**b**) Fibrotic pancreas parenchyma with multiple cysts lined by flat to isoprismatic epithelia (HE, 100×). (**c**) Small groups of acini show a direct connection to the cystic lesion (arrow) (HE, 200×). (**d**) Immunohistochemically, the lesion is positive for Trypsin (HE, 100×)

35.4.2 Lymphoepithelial Cyst

Lymphoepithelial cysts of the pancreas are cystic lesions lined by squamous epithelium with underlying dense lymphoid tissue and lymph follicles (Fig. 35.6a). These lesions are very rare and only few more than 100 cases have been reported in literature so far [49]. They show predominance for middle-aged, male patients and can arise anywhere in the pancreas [50].

Grossly, lymphoepithelial cysts of the pancreas appear as well-demarcated uni- or multilocular cysts with smooth surface lacking prominent projections, but may be filled with keratinous material [50]. Upon histology, the cyst-lining is composed of well-differentiated stratified squamous epithelia, which may be attenuated and, in some cases, even denudated, and can occasionally show foci of transitional differentiation [50]. The underlying lymphoid tissue shows a similar composition as mature lymphatic tissue found in lymph nodes and can contain lymph follicles with germinal centers [50].

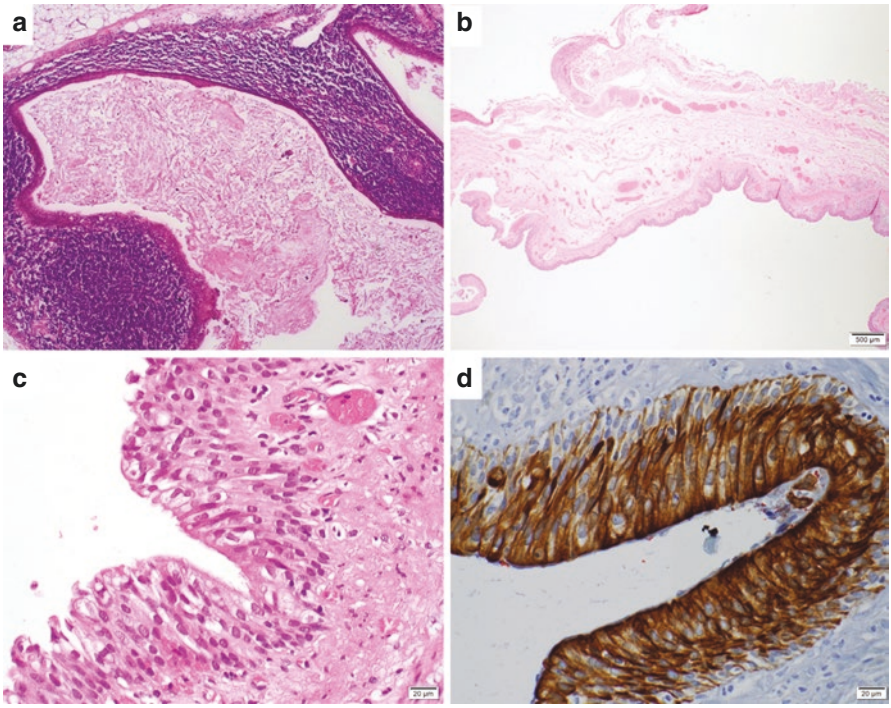

Fig. 35.6 Rare tumor-like lesions of the pancreas. (**a**) **Lymphoepithelial cyst** of the pancreas consisting of stratified squamous epithelium and subepithelial mature lymphoid tissue; the lumen is filled with keratinous material (HE, 50×). (**b**) Wall of a pancreatic **foregut cyst** with stratified epithelium and underlying edematous loose stroma (HE, 20×). (**c**) The epithelium of the foregut cyst consists of columnar ciliated cells (HE, 400×). (**d**) The epithelial cells of the foregut cyst express CK7 in immunohistochemistry (400×). (**e**) **Echinococcus cyst** of the pancreas with a thick fibrous capsule (HE, 20×). (**f**) PAS staining illustrates the layered architecture of the Echinococcus cyst wall (HE, 100×). (**g**) **Pseudolymphoma** of the pancreas displaying prominent lymph follicles with large germinal centers (asterisks). In the bottom part of the picture, atrophic pancreas parenchyma with remnant islets (arrows) can be seen (HE, 5×). Immunohistochemistry for CD20 (**h**, 5×) and CD3 (**i**, 5×) demonstrates organoid distribution of T and B lymphocytes

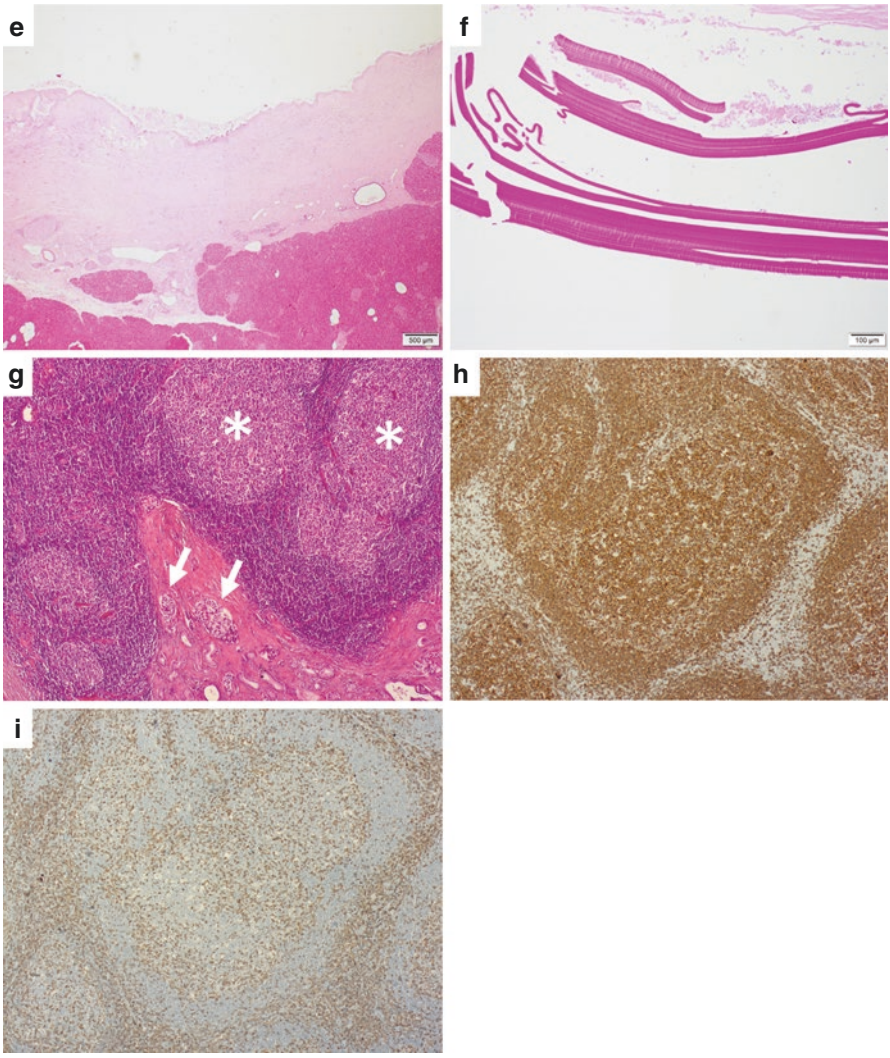

Fig. 35.6 (continued)

The pathogenesis of lymphoepithelial cysts is unknown. So far, proposed hypotheses include: derivation from epithelial remnants in peripancreatic lymph nodes [51], cystically dilated pancreatic ducts with squamous metaplasia [52] and surrounding inflammatory infiltrate, and the possibility that lymphoepithelial cysts of the pancreas may be forms of teratomas or displaced branchial cysts. So far, malignant transformation of lymphoepithelial cysts of the pancreas has not been described.

35.4.3 Dysontogenetic Cyst

Dysontogenetic cysts of the pancreas are congenital cystic lesions, which are mostly diagnosed in children. They either present as solitary cyst or diffusely involve the whole pancreas ("polycystic disease of the pancreas"). The latter can be seen patients with various congenital syndromes associated with cyst formation, such as patients with autosomal-dominant polycystic kidney disease [53], although involvement of the pancreas is very rare and affection of the kidney and liver is much more common. Etiologically, dysontogenetic pancreatic cysts are thought to arise due to abnormalities in the development of pancreatic duct structures during embryogenesis. Very rarely, congenital cysts derived from the foregut may occur in the pancreas. The cyst wall of foregut cysts can contain respiratory glands, cartilage and smooth muscle and is lined by a well-differentiated epithelium including ciliated cells and/or goblet cells (Fig. 35.6b–d) [54].

35.4.4 Parasitic Cyst

Parasitic cysts of the pancreas are very rare, but especially in patients from endemic regions, pancreatic cysts originating from an infection with the helminth *Echinococcus granulosus* or *multilocularis* have been reported. Humans are accidental hosts of *Echinococcus*, which enters the human body in its ovum form via the gastrointestinal tract, penetrates the intestinal wall after hatching to its larva form (oncosphere) and spreads along the portal circulation usually to the liver, although spread to any organ in the body is possible. Here, it forms hydatid cysts which contain immature forms of the worm (protoscolices). The incidence of pancreatic hydatid cysts is reported to be ranging from 0.14% to 2% [55]. Hydatid cysts are typically large cysts which may contain daughter cysts. Histologically, the cyst wall shows an outer laminated acellular membrane and an inner germinal layer, while the cyst lumen contains the protoscolices and their brood capsules (Fig. 35.6e, f). Surrounding tissue commonly shows granulomatous inflammation with increased eosinophilic granulocytes and fibrosis.

Even more rarely than echinococcosis, cystic lesions of the pancreas may be a result of cysticercosis (infection with *Taenia solium*) [56].

35.4.5 Pseudolymphoma

Pseudolymphoma is a localized non-neoplastic proliferation of lymphatic tissue due to exogenic stimuli, such as mechanic tissue injury or foreign bodies, and commonly involves the skin. In the pancreas, pseudolymphoma is extremely rare, and only few single case reports have been published [57–59].

Macroscopically, pseudolymphoma of the pancreas can present as well-described yellow or white mass. Histologically, the lesion shows lymph follicles with polarized germinal centers, consistent with the reactive nature of the lesion (Fig. 35.6g). Normal lymphatic architecture of the tissue can be demonstrated using immunohistochemistry (Fig. 35.6h, i); clonality analysis can further be used to prove the non-neoplastic nature and securely rule out lymphoma.

In pseudolymphomas of other localizations, cases with malignant transformation have been reported. In the pancreas, no malignancy has been detected in the few cases which have been published, with one case showing spontaneous remission [59].

References

1. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011;47(17):2493–511.
2. Gao H, Gao Y, Yin L, et al. Risk factors of the recurrences of pancreatic solid pseudopapillary tumors: a systematic review and meta-analysis. J Cancer. 2018;9(11):1905–14.
3. Sileikis A, Nutautiene V, Seinin D, et al. Solid pseudopapillary neoplasm of the pancreas: analysis of seven cases. Viszeralmedizin. 2014;30(3):211–5.
4. Hu S, Zhang H, Wang X, et al. Asymptomatic versus symptomatic solid pseudopapillary tumors of the pancreas: clinical and MDCT manifestations. Cancer Imaging. 2019;19(1):13.
5. Yu PF, Hu ZH, Wang XB, et al. Solid pseudopapillary tumor of the pancreas: a review of 553 cases in Chinese literature. World J Gastroenterol. 2010;16(10):1209–14.
6. Park JK, Cho EJ, Ryu JK, et al. Natural history and malignant risk factors of solid pseudopapillary tumors of the pancreas. Postgrad Med. 2013;125(2):92–9.
7. Butte JM, Brennan MF, Gonen M, et al. Solid pseudopapillary tumors of the pancreas. Clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg. 2011;15(2):350–7.
8. Brecht IB, Schneider DT, Kloppel G, et al. Malignant pancreatic tumors in children and young adults: evaluation of 228 patients identified through the surveillance, epidemiology, and end result (SEER) database. Klin Pädiatr. 2011;223(6):341–5.
9. Kim CW, Han DJ, Kim J, et al. Solid pseudopapillary tumor of the pancreas: can malignancy be predicted? Surgery. 2011;149(5):625–34.
10. Huang Y, Yang W, Hu J, et al. Diagnosis and treatment of pancreatoblastoma in children: a retrospective study in a single pediatric center. Pediatr Surg Int. 2019;35(11):1231–8.
11. Tanaka Y, Ijiri R, Yamanaka S, et al. Pancreatoblastoma: optically clear nuclei in squamoid corpuscles are rich in biotin. Mod Pathol. 1998;11(10):945–9.
12. Yin SM, Liu YW, Kuo FY, et al. Pancreatoblastoma in adults: a case report and review of literature. HPB. 2018;20:S537.
13. Klimstra DS, Wenig BM, Adair CF, et al. Pancreatoblastoma. A clinicopathologic study and review of the literature. Am J Surg Pathol. 1995;19(12):1371–89.
14. Abraham SC, Wu TT, Klimstra DS, et al. Distinctive molecular genetic alterations in sporadic and familial adenomatous polyposis-associated pancreatoblastomas: frequent alterations in the APC/beta-catenin pathway and chromosome 11p. Am J Pathol. 2001;159(5):1619–27.
15. Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2010;18(1):8–14.
16. Dhebri AR, Connor S, Campbell F, et al. Diagnosis, treatment and outcome of pancreatoblastoma. Pancreatology. 2004;4(5):441–51; discussion 452–3.

17. Defachelles AS, Martin De Lassalle E, Boutard P, et al. Pancreatoblastoma in childhood: clinical course and therapeutic management of seven patients. Med Pediatr Oncol. 2001;37(1): 47–52.
18. Terino M, Plotkin E, Karagozian R. Pancreatoblastoma: an atypical presentation and a literature review. J Gastrointest Cancer. 2018;49(3):361–4.
19. Haugk B, Raman S, Bury Y. Pancreatic pathology: where are we in 2019? Surgery. 2019;37(6):310–8.
20. Salman B, Brat G, Yoon YS, et al. The diagnosis and surgical treatment of pancreatoblastoma in adults: a case series and review of the literature. J Gastrointest Surg. 2013;17(12): 2153–61.
21. *Digestive System Tumours.* WHO Classification of Tumours, 5th Edition, ed. WHO Classification of Tumours Editorial Board. Vol 1. 2019, Lyon.
22. Klimstra DS, Heffess CS, Oertel JE, et al. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol. 1992;16(9):815–37.
23. Cingolani N, Shaco-Levy R, Farruggio A, et al. Alpha-fetoprotein production by pancreatic tumors exhibiting acinar cell differentiation: study of five cases, one arising in a mediastinal teratoma. Hum Pathol. 2000;31(8):938–44.
24. La Rosa S, Adsay V, Albarello L, et al. Clinicopathologic study of 62 acinar cell carcinomas of the pancreas: insights into the morphology and immunophenotype and search for prognostic markers. Am J Surg Pathol. 2012;36(12):1782–95.
25. Lu T, Yang C. Rare case of adult pancreatic hemangioma and review of the literature. World J Gastroenterol. 2015;21(30):9228–32.
26. Naili RE, Nicolas M. Hemangioma of the pancreas: a rare tumor in adults. Am J Clin Pathol. 2015;144(Suppl 2):A350.
27. Mondal U, Henkes N, Henkes D, et al. Cavernous hemangioma of adult pancreas: a case report and literature review. World J Gastroenterol. 2015;21(33):9793–802.
28. Viscosi F, Fleres F, Mazzeo C, et al. Cystic lymphangioma of the pancreas: a hard diagnostic challenge between pancreatic cystic lesions-review of recent literature. Gland Surg. 2018;7(5):487–92.
29. Carvalho D, Costa M, Russo P, et al. Cystic pancreatic lymphangioma - diagnostic role of endoscopic ultrasound. GE Port J Gastroenterol. 2016;23(5):254–8.
30. Dalla Bona E, Beltrame V, Blandamura S, et al. Huge cystic lymphangioma of the pancreas mimicking pancreatic cystic neoplasm. Case Rep Med. 2012;2012:951358.
31. Zhang S, Chen F, Huang X, et al. Perivascular epithelial cell tumor (PEComa) of the pancreas: a case report and review of literature. Medicine (Baltimore). 2017;96(22):e7050.
32. Mizuuchi Y, Nishihara K, Hayashi A, et al. Perivascular epithelial cell tumor (PEComa) of the pancreas: a case report and review of previous literatures. Surg Case Rep. 2016;2(1):59.
33. Mourra N, Lazure T, Colas C, et al. Perivascular epithelioid cell tumor: the first malignant case report in the pancreas. Appl Immunohistochem Mol Morphol. 2013;21(3):e1–4.
34. Degrate L, Misani M, Mauri G, et al. Mature cystic teratoma of the pancreas. Case report and review of the literature of a rare pancreatic cystic lesion. JOP. 2012;13(1):66–72.
35. Liu Z, Tian Y, Xu G, et al. Pancreatic gastrointestinal stromal tumor: clinicopathologic features and prognosis. J Clin Gastroenterol. 2017;51(9):850–6.
36. Yeo SJ, Cho CM, Kwon HJ, et al. An extragastrointestinal stromal tumor originating from the pancreas. Case Rep Gastroenterol. 2018;12(3):671–8.
37. Beltrame V, Gruppo M, Pastorelli D, et al. Extra-gastrointestinal stromal tumor of the pancreas: case report and review of the literature. World J Surg Oncol. 2014;12:105.
38. Paramythiotis D, Kofina K, Bangeas P, et al. Solitary fibrous tumor of the pancreas: case report and review of the literature. World J Gastrointest Surg. 2016;8(6):461–6.
39. Baxter AR, Newman E, Hajdu CH. Solitary fibrous tumor of the pancreas. J Surg Case Rep. 2015;2015(12):rjv144.
40. Sugawara Y, Sakai S, Aono S, et al. Solitary fibrous tumor of the pancreas. Jpn J Radiol. 2010;28(6):479–82.

41. Ambe P, Kautz C, Shadouh S, et al. Primary sarcoma of the pancreas, a rare histopathological entity. A case report with review of literature. World J Surg Oncol. 2011;9:85.
42. Lee C-C, Huang J-C, Shin J-S, et al. Pancreatic sarcoma mimicking pseudocyst after pancreatitis: a case report and review of the literature. J Med Ultrasound. 2015;23:142.
43. Sanei B, Kefayat A, Samadi M, et al. Undifferentiated pleomorphic sarcoma of pancreas: a case report and review of the literature for the last updates. Case Rep Med. 2018;2018:1510759.
44. Zhang H, Jensen MH, Farnell MB, et al. Primary leiomyosarcoma of the pancreas: study of 9 cases and review of literature. Am J Surg Pathol. 2010;34(12):1849–56.
45. Frazier AA. Nonepithelial pancreatic neoplasms: sarcoma versus lymphoma. Radiographics. 2018;38(4):1046.
46. Zamboni G, Terris B, Scarpa A, et al. Acinar cell cystadenoma of the pancreas: a new entity? Am J Surg Pathol. 2002;26(6):698–704.
47. Wang G, Ji L, Qu F-Z, et al. Acinar cell cystadenoma of the pancreas: a retrospective analysis of ten-year experience from a single academic institution. Pancreatology. 2016;16(4):625–31.
48. Singhi AD, Norwood S, Liu TC, et al. Acinar cell cystadenoma of the pancreas: a benign neoplasm or non-neoplastic ballooning of acinar and ductal epithelium? Am J Surg Pathol. 2013;37(9):1329–35.
49. Arumugam P, Fletcher N, Kyriakides C, et al. Lymphoepithelial cyst of the pancreas. Case Rep Gastroenterol. 2016;10(1):181–92.
50. Adsay NV, Hasteh F, Cheng JD, et al. Lymphoepithelial cysts of the pancreas: a report of 12 cases and a review of the literature. Mod Pathol. 2002;15(5):492–501.
51. Arai T, Kino I, Nakamura S, et al. Epidermal inclusions in abdominal lymph nodes. Report of two cases studied immunohistochemically. Acta Pathol Jpn. 1992;42(2):126–9.
52. Truong LD, Stewart MG, Hao H, et al. A comprehensive characterization of lymphoepithelial cyst associated with the pancreas. Am J Surg. 1995;170(1):27–32.
53. Silverman JF, Prichard J, Regueiro MD. Fine needle aspiration cytology of a pancreatic cyst in a patient with autosomal dominant polycystic kidney disease. A case report. Acta Cytol. 2001;45(3):415–9.
54. Gomez Mateo Mdel C, Forner EM, Orti LS, et al. Foregut cystic malformations in the pancreas. Are definitions clearly established? JOP. 2011;12(4):420–4.
55. Shah OJ, Robbani I, Zargar SA, et al. Hydatid cyst of the pancreas. An experience with six cases. JOP. 2010;11(6):575–81.
56. Sharma R, Neogi S. Isolated pancreatic cysticercal cyst presenting as a diagnostic challenge: diagnosis and treatment review. BMJ Case Rep. 2015;2015:bcr2015210774.
57. Nakashiro H, Tokunaga O, Watanabe T, et al. Localized lymphoid hyperplasia (pseudolymphoma) of the pancreas presenting with obstructive jaundice. Hum Pathol. 1991;22(7):724–6.
58. Hatzitheoklitos E, Buchler MW, Friess H, et al. Pseudolymphoma of the pancreas mimicking cancer. Pancreas. 1994;9(5):668–70.
59. Nakata B, Amano R, Matsuoka J, et al. Spontaneously complete regression of pseudolymphoma of the remnant pancreas after pancreaticoduodenectomy. Pancreatology. 2012;12:215–8.

Chapter 36
PET in Pancreatic Cancer

Hulya Wieshmann and K. N. Pannag Desai

Take Home Messages

- Clinical applications of FDG PET CT include diagnosis of malignancy, staging, restaging after treatment, and assessment of tumour response to chemotherapy or radiotherapy, suspected recurrence, differentiation of recurrent or residual malignant disease from therapy-induced changes, study of patients with metastases from unknown primary sites and in radio therapy planning
- FDG PET CT offers better characterisation of mass-forming pancreatitis and therapy induced changes from pancreatic cancer than contrast enhanced CT, based on the distribution and degree of FDG activity
- 18F FDG PET can play an important role in differentiation post therapy changes from recurrence or residual tumour in a post-surgical setting

Pearls and Pitfalls

- PET CT outperforms structural imaging modalities in the detection of distant metastases, allowing for more accurate staging
- Both false-positive and false-negative findings are encountered problems in PET CT imaging.

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- False-negative results can be due to hyperglycaemia, small tumour size or misinterpreting FDG activity in a tumour as physiological FDG activity in adjacent bowel.
- False-positive findings can be a result of misinterpretation of inflammatory changes or misregistration of ^{18}F-FDG activity from the nearby bowel uptake as tumour recurrence.

Further Perspectives

- Future Prospective studies will help to quantify the efficacy and added value of FDG PET CT compared to the diagnostic performance of CT and MRI in the clinical management of patients with pancreatic malignancy

36.1 Introduction

Pancreatic malignancy carries a poor prognosis and approximately 10,000 new patients are diagnosed every year in the United Kingdom. Overall incidence is 12.2 cases per 100,000 persons per year, and it usually presents late, with a 5-year survival rate of 6% at the time of diagnosis [1, 2]. Pancreatic malignancy is a heterogeneous group of neoplasms which includes a range of subtypes. Ninety-six percent of pancreatic cancers are exocrine tumours. The most common type of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) is an exocrine tumour. Cystic neoplasms are less common and include serous and cystic pancreatic tumours (1–2% each) and intrapapillary mucinous neoplasms (3–5%). Epithelial and mixed-differentiation tumours consist of solid pseudopapillary neoplasms (1–2%), neuroendocrine tumours (1–2%), and pancreatoblastoma (<1%) [1]. Computer tomography (CT) and magnetic resonance imaging (MRI) are the main structural imaging modalities used for diagnosis, staging and restaging of pancreatic malignancies. Functional imaging with Positron Emission Tomography (PET) CT or PET MRI can provide added value to structural imaging in the evaluation and management of pancreatic malignancies including PDAC. There are now newer data in the literature available which support and highlight the advantages, limitations, and pitfalls of functional imaging in the evaluation of pancreatic malignancies.

36.2 Positron Emission Tomography

PET is a non-invasive diagnostic tool which is based on the use of different substances of biological interest (sugars, amino acids, metabolic precursors, and hormones) labelled with positron emitting radioisotopes (PET radiopharmaceuticals).

The most widely used tracer ^{18}F-Fluorodeoxyglucose (FDG) is an analogue of glucose. In 1930 Otto Warburg described that malignant tissue utilises glucose at greater rates than normal tissue, mainly by glycolysis "Otto Warburg effect" [3]. FDG is taken up by normal and tumourous cells via the first stages of normal glucose pathway. Unlike glucose, however, after initial phosphorylation into FDG-6-phosphate, FDG cannot undergo further metabolism and accumulates in tumour cells. This relationship has been utilised to develop an imaging method that maps changes in functional activity in the malignant cells by labelling FDG with the radioactive positron emitter 18-Fluorine (18F-FDG). The concentration of radioactivity in malignant cells is proportional to the rate of glucose utilisation. Metabolic changes induced by tumour growth precede structural changes and functional imaging with 18F-FDG allows detecting malignant tissue which is not evident on conventional morphological diagnostic modalities such as CT, MRI and Ultrasound. A review of the FDG-PET oncology literature from 1993 to 2000 by Gambhir et al. [4] illustrated the added value of FDG-PET in the clinical management of cancer patients and as a biomarker of disease prognosis and progression. At present there is considerable evidence that FDG-PET has a role in the diagnostic assessment of patients with suspected malignancies. The current oncological applications include diagnosis of malignancy, staging, restaging after treatment, assessment of tumour response to chemotherapy or radiotherapy, suspected recurrence without clinical, biochemical or morphological imaging evidence, differentiation of recurrent or residual malignant disease from therapy-induced changes, study of patients with metastases from unknown primary sites and in radio therapy planning.

In pancreatic malignancy, structural imaging in the assessment of tumour diagnosis and recurrence is a radiological challenge. After treatment, the surgical changes with distortion of the normal anatomy can make the distinction between post therapy changes and recurrence or residual tumour difficult. Furthermore, physiological or reactive nodes in the abdomen can result in equivocal reports. In these situations, PET with 18F FDG is a better imaging technique than either CT or MRI (Figs. 36.1, 36.2, 36.3, 36.4 and 36.5).

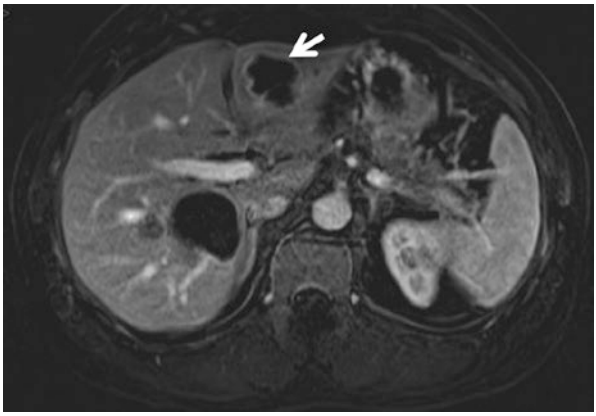
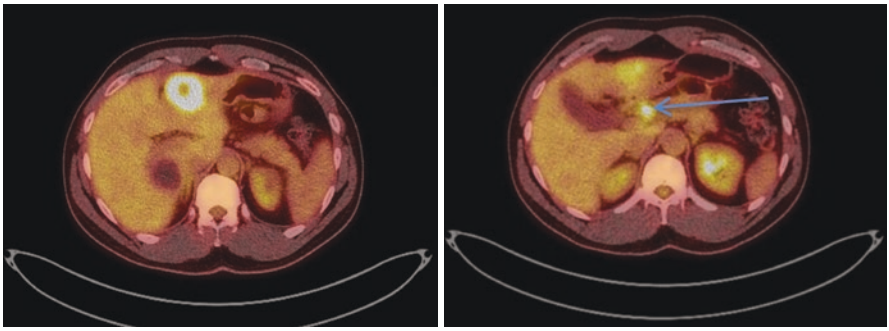
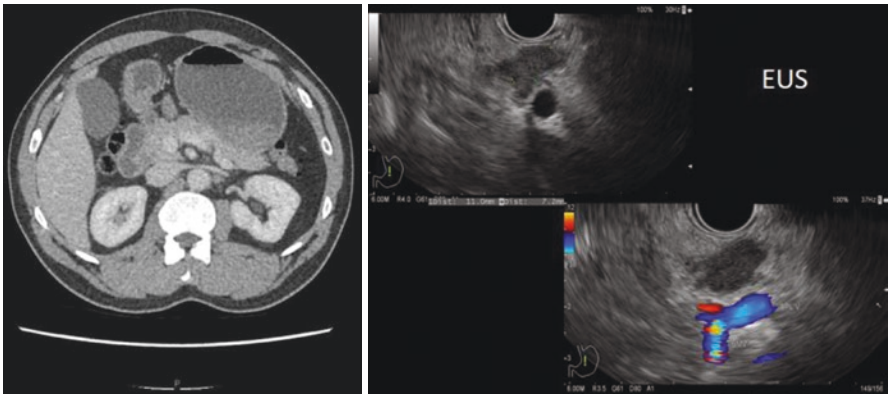


Fig. 36.1 Contrast enhanced MRI of a patient presenting clinically with vague abdominal pain and weight loss shows a peripherally enhancing liver lesion in segment 2/3 with the imaging characteristics of a possible cholangiocarcinoma and a liver cyst in segment 6



Figs. 36.2 and 36.3 Staging PET CT demonstrates increased FDG activity at the level of the liver lesion shown on MRI. In addition there is an abnormal FDG focus in the region of the pancreatic head



Figs. 36.4 and 36.5 No visible structural abnormality can be identified on the portal venous phase contrast enhanced CT image to correspond to the focal FDG activity shown on PET CT. The subsequent EUS demonstrates a 7.2 × 11 mm sized hypoechoic lesion in the pancreas corresponding to the area of focal FDG activity shown on PET CT

Hybrid imaging devices where CT or MRI is integrated with PET on a single gantry allow accurate anatomic delineation of FDG-avid lesions, improving overall image interpretation, accuracy, and confidence. Intravenous contrast may be necessary to assess accurately for vascular evaluation, lesion depiction, characterisation, and local staging for surgical planning [5].

36.3 Pancreatic Cancer

Diagnosis and treatment of pancreatic cancer continue to be challenging. Contrast-enhanced CT and MRI including magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) and ^{18}F-Fluorodeoxyglucose positron

Table 36.1 PET vs. CT/MRI

	PET	CT/MRI
Anatomical details	Poor depiction due to low. Spatial resolution	Better depicted
Biological/metabolic activity	Functional imaging, hence depicts cellular activity	Non-functional imaging
Preparation for study	Low carbohydrate diet, refrain from strenuous physical activity prior to test	Standard bowel preparation
Radiation dose	Relatively higher	Relatively lower in CT, no radiation in MRI
Primary tumour	Low sensitivity in detecting <1 cm tumours	Relatively higher sensitivity in detecting <1 cm tumours
Distant metastases/ nodal metastases	Higher sensitivity in detecting	Lower sensitivity
Recurrence vs. post therapy change	Better differentiation	Poor in differentiating between the two.

emission tomography (FDG PET CT) are the recognized imaging modalities available for diagnosis and staging of pancreatic cancer (Table 36.1).

Surgical resection is the only curative treatment for non-metastatic pancreatic cancer, thus making it mandatory to assess meticulously for the presence or absence of metastases and their relationship to the surrounding vascular structures [6]. In patients with locally advanced pancreatic cancer, induction chemotherapy followed by chemo-radiotherapy is a palliative option [7, 8]. Patients with metastatic spread to the liver, peritoneum, and regional lymph nodes, are best treated with chemotherapy alone or other palliative therapies [7].

FDG PET CT and FDG PET MRI have been shown to have an added value in the management of pancreatic cancer. The potential indications for FDG PET CT or FDG PET MRI include image guided targeted biopsy planning in patients with suspected pancreatic cancer and equivocal CT or non-diagnostic fine-needle aspiration findings, tumour staging, evaluating tumour recurrence, and monitoring response to therapy.

Tatli et al. [9] confirmed that the use of previously acquired FDG PET CT images that are registered with intraprocedural CT to guide targeted biopsy in the abdomen is feasible and improves the diagnostic success of CT-guided biopsy of intra-abdominal lesions.

36.3.1 Equivocal Cross-Sectional Imaging

There are limitations of CT for depicting pancreatic cancer with a correlation between tumour size and sensitivity (83% for depicting lesions <2 cm) [10]. Through a combined qualitative and semi-quantitative evaluation, FDG PET CT provides additional information [11]. Pancreatic cancer manifests as an area of increased FDG uptake, appearing as a "hot spot" within the pancreas [3–5, 11]. On

the basis of tumour biology and the degree of desmoplastic response, pancreatic cancer may demonstrate a low level or no FDG uptake.

Semi-quantitative analysis depends on calculating the Standard Uptake Value (SUV) of the lesion on the basis of activity in the region of interest [11]. Typically, the maximum SUV (SUV_{max}) is higher in malignant lesions, irrespective of the tumour size (above a subcentimetre minimum size threshold) [12, 13]. Thus, FDG PET may be useful in depicting small pancreatic lesions (<2 cm) or iso-attenuating lesions, which are difficult to detect on CT or MRI, as well as for lesion characterisation [3–5, 14]. Okano et al. [13] support the use of FDG PET for depicting small pancreatic lesions, with reported sensitivities of 100% for FDG PET and 40% for contrast-enhanced CT for depicting lesions smaller than 2 cm. Lemke et al. [15] found that fused contrast-enhanced PET CT is more sensitive for tumour depiction than PET and CT alone.

FDG PET CT was first used to differentiate chronic pancreatitis from pancreatic malignancy. Both conditions demonstrate extensive fibrosis, with overlapping imaging findings. With chronic pancreatitis, the organ demonstrates diffuse but lower FDG uptake versus the more focal uptake and higher maximum SUV (SUV_{max}) seen with tumour involvement [1, 14]. Differentiating mass-forming pancreatitis (MFP) from pancreatic cancer remains a diagnostic dilemma, even with contrast enhanced CT. PET CT offers better characterisation of mass-forming pancreatitis from pancreatic cancer than contrast enhanced CT [12, 14, 16], based on the distribution and degree of FDG activity.

Earlier studies reported that pancreatic cancer tends to demonstrate higher FDG uptake than MFP. The SUV of PDAC (3.5–5.1 ± 1.6–2.6) was higher than that of benign lesions (1.9–0.8 ± 0.6–1.7) and the normal pancreas [12, 17]. Focal FDG activity can be highly suspicious for cancer and requires further investigation, whereas in patients who are euglycemic, a lack of FDG uptake is more indicative of an MFP lesion [14, 18]. In a study of patients with suspected pancreatic cancer, the SUV_{max} of malignant tumours was distinctly higher than that of benign lesions and chronic pancreatitis; FDG PET CT had a sensitivity and specificity of 89% and 74%, respectively, for depicting such lesions [12]. In another study of 38 patients, four had an MFP lesion that demonstrated no FDG uptake on PET CT [16].

36.4 Preoperative Staging

Accurate staging of pancreatic cancer is essential to delineate the relationship of the primary tumour with surrounding structures and assess for distant spread of disease. Spread to regional or distant lymph nodes is usually indicative of a poor prognosis and usually renders the cancer inoperable [19]. Multi-slice CT is an excellent imaging tool to assess for local spread, with a positive predictive value of 73–91% for resectability and 95–100% for non-resectability [16, 20–27]. However small volume liver or peritoneal spread can be difficult to detect on CT and are discovered during surgery in about 20% of patients with tumours who

were thought to be resectable on staging CT. Likewise, lymph node spread is not optimally studied with CT.

36.4.1 Characterization of Lymph Nodes

Spread to lymph nodes is common and indicates a poor outcome [7, 19]. Lymph node staging remains difficult with CT, with a dismal 37% sensitivity and a more acceptable 79% specificity [28]. Some studies reported moderate improvement in the performance of FDG PET compared with multi-slice CT in patients with pancreatic lesions, with a sensitivity and specificity ranging from 30% to 49% and 63–93%, respectively, for evaluation of lymph nodes [11, 16, 29, 30]. The performance of PET CT for nodal staging in patients with pancreatic cancer has not been appropriately studied. The combination of PET and CT may improve the specificity of nodal staging compared with CT alone, helping identify metastatic deposits in lymph nodes that demonstrate nonspecific or borderline enlargement at CT.

36.4.2 Depiction of Metastases

Identification and characterisation of indeterminate hepatic lesions is challenging in patients with a fatty liver or contraindications for contrast material. Increased FDG activity in hepatic lesions is a strong indication of malignancy, and a lack of FDG uptake usually supports benignity. However, malignancy cannot be completely excluded in the absence of FDG uptake, especially in small lesions [31]. Moreover, the performance of PET is influenced not only by the size of a lesion, but also by its biologic or histopathologic type and whether the patient has undergone therapy for the tumour [32]. In a study comparing the performance of hepatobiliary contrast-enhanced MRI and FDG PET, MRI was more accurate in depicting small liver metastases, with a reported accuracy of 97.1% compared with 85.3% for FDG PET [33]. However, for depiction of distant metastases, FDG PET is superior to contrast-enhanced CT and MRI, with a reported sensitivity of 88% [16].

Pancreatic cancer tends to metastasize to the peritoneum thus rendering patients ineligible for surgery or locoregional treatment [34]. Detection of peritoneal deposits is challenging on CT, with a sensitivity of 65–88% and specificity of 38–63% [35]. In 7% of patients where the multi-slice CT showed no evidence of metastases, peritoneal deposits were found at staging laparoscopy and had locally non-resectable disease [20, 34–36].

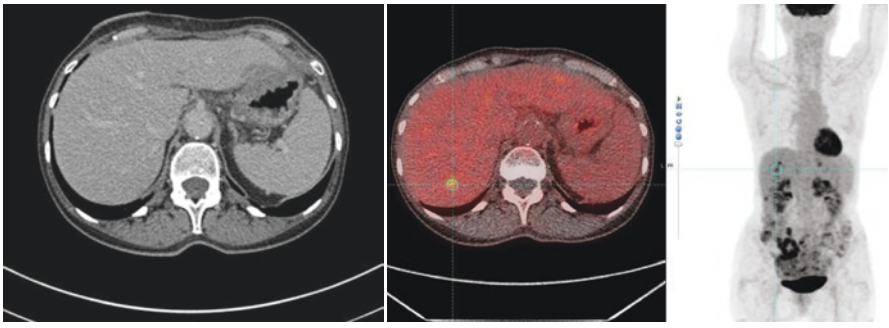
FDG PET for preoperative pancreatic cancer staging has been reported to be cost beneficial because of its depiction of unexpected distant metastases in 43% of patients, thereby avoiding unnecessary surgical procedures [29, 33, 37]. The use of FDG PET CT may improve patient selection for surgery by detecting the primary pancreatic tumours not clearly evident on CT or MRI and prevent unnecessary

pancreatic resections by detecting unsuspected metastases [16, 27] in as many as 25% of patients.

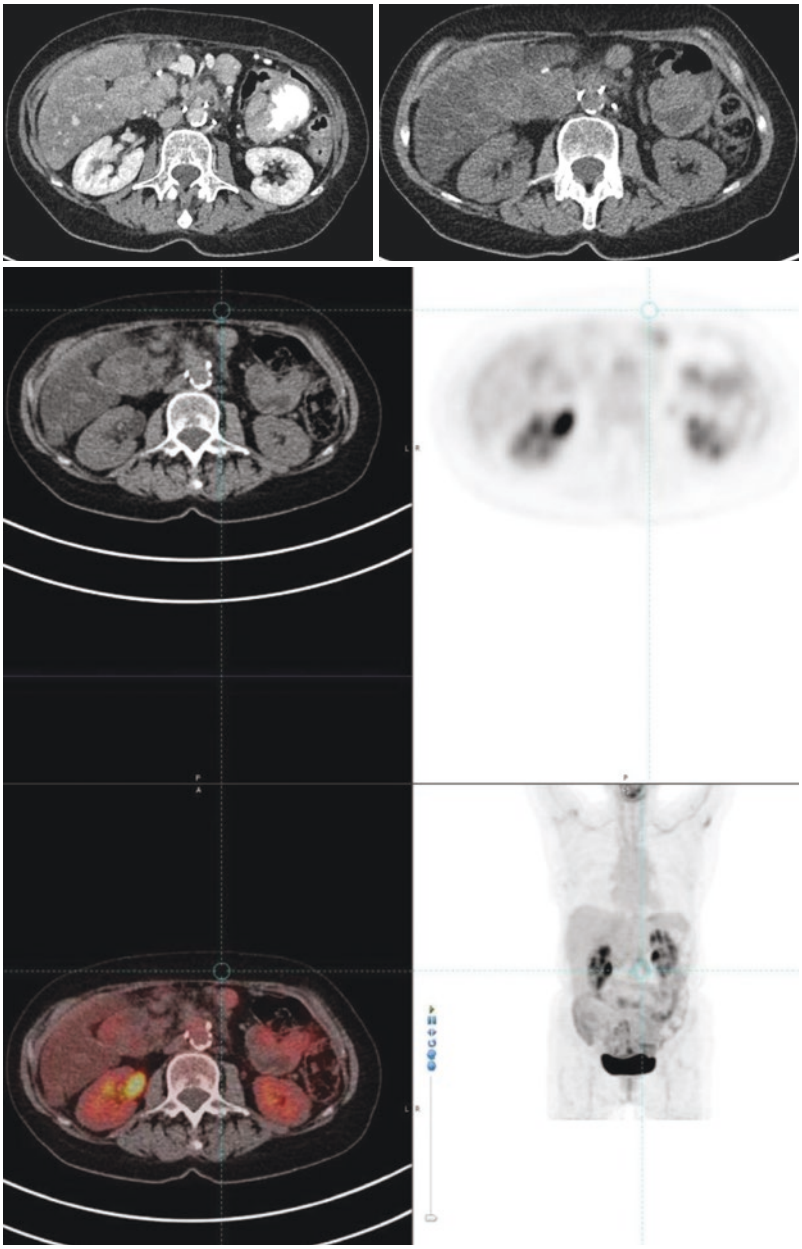
36.4.3 Depiction of Tumour Recurrence and Monitoring Response to Therapy

After surgery, 72–92% of pancreatic cancer recur locally within 2 years [38–40]. Locally recurrent tumors are usually not resectable; however, radiation therapy or ablation (e.g. radiofrequency or cryoablation) may be a palliative option. The postoperative changes in the surgical bed and early tumour recurrence can have similar morphologic appearances and reliable differentiation between these entities is difficult on CT [38, 41–43]. Increased FDG activity 3 months following tumour resection within the surgical bed is usually not an expected finding and suggestive of recurrence. The reported sensitivity of FDG PET for depicting tumour recurrence (Figs. 36.6 and 36.7) is 96% compared with 39% for CT and MRI [41]. Moreover, after resection, tumor relapse is depicted at FDG PET earlier than it is at CT, with high sensitivity (98%) and specificity (90%) [38].

FDG PET may play a role in monitoring response to chemo and radiation therapy in patients with unresectable pancreatic cancer [42, 44, 45]. As with other neoplasms, a significant reduction in FDG uptake may precede volumetric reduction on structural imaging and may be proportional to the change in tumour size at subsequent follow-up examinations (Figs. 36.8, 36.9, 36.10). Therefore, earlier depiction of tumour response to therapy on FDG PET could influence the continuation or withdrawal of treatment [44]. Some recently published studies reported that FDG PET CT may have prognostic value because tumours with a higher baseline SUV_{max} are more likely to recur in the early postoperative period. SUV_{max} is also an independent predictor for overall survival in patients with locally advanced pancreatic cancer [41, 44, 46–48].



Figs. 36.6 and 36.7 FDG PET CT in a patient with previously resected pancreatic cancer and clinically suspected recurrence showing multiple liver metastases not distinctly visualised on contrast enhanced CT



Figs. 36.8–36.10 Pre-treatment contrast enhanced showing excess tissue in the abdomen at the level of the SMA in a patient with pancreatic cancer. On post treatment CT there is still residual excess tissue and it is not possible to determine whether this represents ongoing malignancy. The subsequent post-treatment. PET CT shows normal FDG distribution including at the level of the residual excess tissue surrounding the SMA

36.5 Differential Diagnosis

36.5.1 Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumours (PNETs) represent 1–2% of all pancreatic neoplasms [49, 50]. Most PNETs express Somatostatin receptors (SSRs), which can be utilised for both diagnostic and therapeutic purposes. The most often used PET tracers to assess PNET's for expression of SSR are ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE. However in pancreatic cancer there is usually no SSR expression and ^{18}F-FDG is the choice of tracer in PET imaging [51–61]. Well-differentiated, slow-growing neuroendocrine tumours demonstrate little or no FDG uptake, whereas pancreatic cancer, metastases and poorly differentiated neuroendocrine tumours, are well depicted on FDG PET.

36.5.2 Pancreatic Lymphoma

Lymphoma may arise primarily in the pancreas or secondarily involve the pancreas in the setting of systemic disease. Primary pancreatic lymphoma is rare (accounting for 0.5% of all pancreatic neoplasms) and is usually of the non-Hodgkin type, with both B- and T-cell lineages. The pancreatic head is the most common location, although the entire gland may be affected [49, 62].

The usefulness of FDG PET in staging and differentiating primary pancreatic lymphoma from secondary lymphoma has already been established [63, 64].

Upon completion of chemo or radiation therapy, response to therapy may be assessed at PET CT. Persistent FDG uptake in the pancreas or lymph nodes is indicative of residual disease, whereas a lack of FDG uptake is indicative of a complete metabolic response. FDG PET findings may also be used to determine whether a favourable progression-free survival is likely. Two studies reported a 5-year progression-free survival rate of 88.8% in patients with negative PET findings and only 16.2% in patients with positive PET findings [65, 66].

36.5.3 Metastases

Pancreatic metastases are rare, accounting for 2% of all pancreatic neoplasms [49, 67]. The primary malignancies that most commonly metastasize to the pancreas are lung, breast, melanoma, gastric, colorectal, renal, and ovarian cancers [49, 68].

Most pancreatic metastases are hypoattenuating with variable contrast enhancement, and on FDG PET they often demonstrate uptake similar to that in the primary tumour [69]. Sato et al. [68] reported that in patients with lung cancer, FDG PET CT is advantageous both in the first stage and the follow-up stage in

depicting unsuspected pancreatic metastases that have not yet manifested on structural imaging.

36.6 Cystic Neoplasms

Cystic neoplasms of the pancreas constitute less than 10% of all pancreatic neoplasms. They encompass a wide range of pathologic conditions ranging from benign lesions, such as serous cystoadenomas, to malignant, potentially malignant, and borderline tumours, such as neuroendocrine tumours with cystic features, mucinous cystic neoplasms, and IPMNs [70]. Contrast-enhanced CT and MRI are the preferred modalities for the initial evaluation of cystic lesions. However, given the overlap in features of various cystic lesions, accurate classification and determination of benignity or malignancy is not always possible [71–73].

Published studies have shown that FDG-positive cystic neoplasms are frankly malignant or invasive. Conversely, FDG-negative lesions may be benign, borderline malignant, or non-invasive malignant [74]. By using a cut-off SUV of 2.5, differentiating between benign and malignant IPMNs was feasible, with malignant lesions (range, 2.7–6.7) demonstrating significantly higher SUV_{max} than benign lesions (range, 2.1–1.8) [71, 75, 76]. The sensitivity (94%) and specificity (100%) of PET CT for depicting malignant cystic pancreatic lesions have been shown to be superior to those of FDG PET (56% sensitivity and 83% specificity) and CT (81% sensitivity and 100% specificity) [77].

It has been suggested that the combination of the morphologic features of cystic lesions seen at multidetector CT and the concurrent functional information of FDG uptake provided by PET may improve diagnosis of malignant or invasive mucinous neoplasms of the pancreas [71, 75, 76].

36.7 Limitations

False-positive and false-negative results occur with FDG PET and its inherent low spatial resolution may interfere with precise anatomic localisation of findings [4, 5]. The reported sensitivity and specificity of FDG PET for depiction of pancreatic adenocarcinoma are 46–71% and 63–100%, respectively [16]. It has been reported that, among patients with pancreatic malignancy, FDG PET has a relatively better sensitivity (83–86%) for tumour depiction in patients who are euglycemic than in those with elevated glucose levels (42–69%) [3–5, 78]. Relatively high levels of ionizing radiation are also a consideration in whole-body PET. Likewise, long scanning times may affect patient compliance and increase patient motion. Finally, quantification and reproducibility of SUV may be inaccurate because of noise attenuation correction methods and different reconstruction platforms.

36.8 Conclusion

FDG PET CT plays an important part in the management of pancreatic cancer patients. The combination of functional and anatomical information provided by PET CT improves the depiction of the biological behaviour of the tumour, compared with other conventional imaging modalities. PET CT outperforms structural imaging modalities in the detection of distant metastases, allowing for more accurate staging.

References

1. SEER stat fact sheets: pancreas cancer. Surveillance, Epidemiology, and End Results Program website. http://seer.cancer.gov/statfacts/html/pancreas.html. Updated June 14, 2013.
2. Michl P, Pauls S, Gress TM. Evidence-based diagnosis and staging of pancreatic cancer. Best Pract Res Clin Gastroenterol. 2006;20:227–51.
3. Warburg O, Posener K, Negelein E. On the metabolism of cancer cells. Biochem Z. 1924;152:319–44.
4. Gambhir SS, Czernin J, Schwimmer J, et al. A tabulated summary of the FDGPET literature. J Nucl Med. 2001;42:1–93S.
5. Sokoloff L. The deoxyglucose method: theory and practice. Eur Neurol. 1981;20:137–45.
6. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
7. Duffy JP, Reber HA. Nonendocrine tumors of the pancreas. In: Yamada T, editor. Textbook of gastroenterology. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2003. p. 2091–107.
8. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol. 2009;27(13):2269–77.
9. Tatli S, Gerbaudo VH, Mamede M, Tuncali K, Shyn PB, Silverman SG. Abdominal masses sampled at PET/CT-guided percutaneous biopsy: initial experience with registration of prior PET/CT images. Radiology. 2010;256(1):305–11.
10. Tamm EP, Loyer EM, Faria SC, Evans DB, Wolff RA, Charnsangavej C. Retrospective analysis of dual-phase MDCT and follow-up EUS/EUS-FNA in the diagnosis of pancreatic cancer. Abdom Imaging. 2007;32(5):660–7.
11. Higashi T, Saga T, Nakamoto Y, et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET): usefulness and limitations in "clinical reality". Ann Nucl Med. 2003;17(4):261–79.
12. Schick V, Franzius C, Beyna T, et al. Diagnostic impact of 18F-FDG PET-CT evaluating solid pancreatic lesions versus endosonography, endoscopic retrograde cholangio-pancreatography with intraductal ultrasonography and abdominal ultrasound. Eur J Nucl Med Mol Imaging. 2008;35(10):1775–85.
13. Okano K, Kakinoki K, Akamoto S, et al. 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer. World J Gastroenterol. 2011;17(2):231–5.
14. van Kouwen MC, Jansen JB, van Goor H, de Castro S, Oyen WJ, Drenth JP. FDG-PET is able to detect pancreatic carcinoma in chronic pancreatitis. Eur J Nucl Med Mol Imaging. 2005;32(4):399–404.

15. Lemke AJ, Niehues SM, Hosten N, et al. Retrospective digital image fusion of multidetector CT and 18F-FDG PET: clinical value in pancreatic lesions—a prospective study with 104 patients. J Nucl Med. 2004;45(8):1279–86.
16. Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg. 2009;250:957–63.
17. Koyama K, Okamura T, Kawabe J, et al. Diagnostic usefulness of FDG PET for pancreatic mass lesions. Ann Nucl Med. 2001;15(3):217–24.
18. Imdahl A, Nitzsche E, Krautmann F, et al. Evaluation of positron emission tomography with 2-[18F]fluoro-2-deoxy-d-glucose for the differentiation of chronic pancreatitis and pancreatic cancer. Br J Surg. 1999;86(2):194–9.
19. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007;246(1):52–60.
20. Vargas R, Nino-Murcia M, Trueblood W, Jeffrey RB. MDCT in pancreatic adenocarcinoma: prediction of vascular invasion and resectability using a multiphasic technique with curved planar reformations. AJR Am J Roentgenol. 2004;182(2):419–25.
21. Zamboni GA, Kruskal JB, Vollmer CM, Baptista J, Callery MP, Raptopoulos VD. Pancreatic adenocarcinoma: value of multidetector CT angiography in preoperative evaluation. Radiology. 2007;245(3):770–8.
22. Fukushima H, Itoh S, Takada A, et al. Diagnostic value of curved multiplanar reformatted images in multislice CT for the detection of resectable pancreatic ductal adenocarcinoma. Eur Radiol. 2006;16(8):1709–18.
23. Diehl SJ, Lehmann KJ, Sadick M, Lachmann R, Georgi M. Pancreatic cancer: value of dual-phase helical CT in assessing resectability. Radiology. 1998;206(2):373–8.
24. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. AJR Am J Roentgenol. 1997;168(6):1439–43.
25. Manak E, Merkel S, Klein P, Papadopoulos T, Bautz WA, Baum U. Resectability of pancreatic adenocarcinoma: assessment using multidetector-row computed tomography with multiplanar reformations. Abdom Imaging. 2009;34(1):75–80.
26. Valls C, Andía E, Sanchez A, et al. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. AJR Am J Roentgenol. 2002;178(4):821–6.
27. Saif MW, Cornfeld D, Modarresifar H, Ojha B. 18F-FDG positron emission tomography CT (FDG PET-CT) in the management of pancreatic cancer: initial experience in 12 patients. J Gastrointest Liver Dis. 2008;17(2):173–8.
28. Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol. 2004;99(3):492–501.
29. Heinrich S, Goerres GW, Schäfer M, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005;242(2):235–43.
30. Diederichs CG, Staib L, Vogel J, et al. Values and limitations of 18F-fluorodeoxyglucose-positron-emission tomography with preoperative evaluation of patients with pancreatic masses. Pancreas. 2000;20(2):109–16.
31. Nakamoto Y, Higashi T, Sakahara H, et al. Contribution of PET in the detection of liver metastases from pancreatic tumours. Clin Radiol. 1999;54(4):248–52.
32. Akhurst T, Kates TJ, Mazumdar M, et al. Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol. 2005;23(34):8713–6.

33. Sahani DV, Kalva SP, Fischman AJ, et al. Detection of liver metastases from adenocarcinoma of the colon and pancreas: comparison of mangafodipir trisodium-enhanced liver MRI and whole-body FDG PET. AJR Am J Roentgenol. 2005;185(1):239–46.
34. Liu RC, Traverso LW. Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by computed tomography. Surg Endosc. 2005;19(5):638–42.
35. Tabuchi T, Itoh K, Ohshio G, et al. Tumor staging of pancreatic adenocarcinoma using early- and late-phase helical CT. AJR Am J Roentgenol. 1999;173(2):375–80.
36. Nishiyama Y, Yamamoto Y, Yokoe K, et al. Contribution of whole body FDG-PET to the detection of distant metastasis in pancreatic cancer. Ann Nucl Med. 2005;19(6):491–7.
37. Delbeke D, Rose DM, Chapman WC, et al. Optimal interpretation of FDG PET in the diagnosis, staging and management of pancreatic carcinoma. J Nucl Med. 1999;40(11):1784–91.
38. Sperti C, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. Tumor relapse after pancreatic cancer resection is detected earlier by 18-FDG PET than by CT. J Gastrointest Surg. 2010;14(1):131–40.
39. Kleeff J, Reiser C, Hinz U, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg. 2007;245(4):566–72.
40. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med. 2003;139(11):879–92.
41. Ruf J, Lopez Hänninen E, Oettle H, et al. Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. Pancreatology. 2005;5(2-3):266–72.
42. Kuwatani M, Kawakami H, Eto K, et al. Modalities for evaluating chemotherapeutic efficacy and survival time in patients with advanced pancreatic cancer: comparison between FDG-PET, CT, and serum tumor markers. Intern Med. 2009;48(11):867–75.
43. Casneuf V, Delrue L, Kelles A, et al. Is combined 18F-fluorodeoxyglucose-positron emission tomography/computed tomography superior to positron emission tomography or computed tomography alone for diagnosis, staging and restaging of pancreatic lesions? Acta Gastroenterol Belg. 2007;70(4):331–8.
44. Yoshioka M, Sato T, Furuya T, et al. Role of positron emission tomography with 2-deoxy-2-[18F]fluoro-d-glucose in evaluating the effects of arterial infusion chemotherapy and radiotherapy on pancreatic cancer. J Gastroenterol. 2004;39(1):50–5.
45. Bang S, Chung HW, Park SW, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. J Clin Gastroenterol. 2006;40(10):923–9.
46. Schellenberg D, Quon A, Minn AY, et al. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. Int J Radiat Oncol Biol Phys. 2010;77(5):1420–5.
47. Okamoto K, Koyama I, Miyazawa M, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts early recurrence after pancreatic cancer resection. Int J Clin Oncol. 2011;16(1):39–44.
48. Blake MA, Singh A, Setty BN, et al. Pearls and pitfalls in interpretation of abdominal and pelvic PET-CT. Radiographics. 2006;26(5):1335–53.
49. Hruban RH, Klimstra DS, Pitman MB. AFIP atlas of tumor pathology: tumors of the pancreas—series 4. Washington, DC: AFIP; 2007. p. 23–376.
50. Tan EH, Tan CH. Imaging of gastroenteropancreatic neuroendocrine tumors. World J Clin Oncol. 2011;2(1):28–43.
51. Massironi S, Sciola V, Peracchi M, Ciafardini C, Spampatti MP, Conte D. Neuroendocrine tumors of the gastro-entero-pancreatic system. World J Gastroenterol. 2008;14:5377–84.
52. Ehehalt F, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. Oncologist. 2009;14:456–67.
53. Bombardieri E, Maccauro M, De Deckere E, Savelli G, Chiti A. Nuclear medicine imaging of neuroendocrine tumours. Ann Oncol. 2001;12(Suppl 2):S51–61.

54. Ichikawa T, Peterson MS, Federle MP, et al. Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. Radiology. 2000;216(1):163–71.
55. Nakamoto Y, Higashi T, Sakahara H, et al. Evaluation of pancreatic islet cell tumors by fluorine-18 fluorodeoxyglucose positron emission tomography: comparison with other modalities. Clin Nucl Med. 2000;25(2):115–9.
56. Rufini V, Baum RP, Castaldi P, et al. Role of PET/CT in the functional imaging of endocrine pancreatic tumors. Abdom Imaging. 2012;37:1004–20.
57. van Essen M, Sundin A, Krenning EP, Kwekkeboom DJ. Neuroendocrine tumours: the role of imaging for diagnosis and therapy. Nat Rev Endocrinol. 2014;10:102–14.
58. Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol. 2008;26:1489–95.
59. Orlefors H, Sundin A, Garske U, et al. Whole-body (11) C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Clin Endocrinol Metab. 2005;90:3392–400.
60. Binderup T, Knigge U, Loft A, et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med. 2010;51:704–12.
61. Bhate K, Mok WY, Tran K, Khan S, Al-Nahhas A. Functional assessment in the multimodality imaging of pancreatic neuro-endocrine tumours. Minerva Endocrinol. 2010;35:17–25.
62. Nayer H, Weir EG, Sheth S, Ali SZ. Primary pancreatic lymphomas: a cytopathologic analysis of a rare malignancy. Cancer. 2004;102(5):315–21.
63. Karam M, Novak L, Cyriac J, Ali A, Nazeer T, Nugent F. Role of fluorine-18 fluorodeoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. Cancer. 2006;107(1):175–83.
64. Martin DR, Semelka RC. MR imaging of pancreatic masses. Magn Reson Imaging Clin N Am. 2000;8(4):787–812.
65. Yoon SN, Lee MH, Yoon JK. F-18 FDG positron emission tomography findings in primary pancreatic lymphoma. Clin Nucl Med. 2004;29(9):574–5.
66. Mikhaeel NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. Ann Oncol. 2005;16(9):1514–23.
67. Ghavamian R, Klein KA, Stephens DH, et al. Renal cell carcinoma metastatic to the pancreas: clinical and radiological features. Mayo Clin Proc. 2000;75(6):581–5.
68. Sato M, Okumura T, Kaito K, et al. Usefulness of FDG-PET/CT in the detection of pancreatic metastases from lung cancer. Ann Nucl Med. 2009;23(1):49–57.
69. Merkle EM, Boaz T, Kolokythas O, Haaga JR, Lewin JS, Brambs HJ. Metastases to the pancreas. Br J Radiol. 1998;71(851):1208–14.
70. Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. N Engl J Med. 2004;351(12):1218–26.
71. Hong HS, Yun M, Cho A, et al. The utility of F-18 FDG PET/CT in the evaluation of pancreatic intraductal papillary mucinous neoplasm. Clin Nucl Med. 2010;35(10):776–9.
72. Takeshita K, Kutomi K, Takada K, et al. Unusual imaging appearances of pancreatic serous cystadenoma: correlation with surgery and pathologic analysis. Abdom Imaging. 2005;30(5):610–5.
73. Sahani DV, Sainani NI, Blake MA, Crippa S, Mino-Kenudson M. del-Castillo CF. Prospective evaluation of reader performance on MDCT in characterization of cystic pancreatic lesions and prediction of cyst biologic aggressiveness. AJR Am J Roentgenol. 2011;197(1):W53–61.
74. Sperti C, Bissoli S, Pasquali C, et al. 18-fluorodeoxyglucose positron emission tomography enhances computed tomography diagnosis of malignant intraductal papillary mucinous neoplasms of the pancreas. Ann Surg. 2007;246(6):932–7; discussion 937–9.

75. Takanami K, Hiraide T, Tsuda M, et al. Additional value of FDG PET/CT to contrast-enhanced CT in the differentiation between benign and malignant intraductal papillary mucinous neoplasms of the pancreas with mural nodules. Ann Nucl Med. 2011;25(7):501–10.
76. Tomimaru Y, Takeda Y, Tatsumi M, et al. Utility of 2-[18F] fluoro-2-deoxy-d-glucose positron emission tomography in differential diagnosis of benign and malignant intraductal papillary-mucinous neoplasm of the pancreas. Oncol Rep. 2010;24(3):613–20.
77. Sainani N, Sahani DV, Blake M, Deshpande V, Fernandes-del Castillo C, Fischman A. Morphological and functional characterization of mucinous lesions of pancreas: is the combination PET-CT better than MDCT or PET alone? J Nucl Med Meet Abst. 2008;49:273P-a.
78. Diederichs CG, Staib L, Glatting G, Beger HG. Reske SN FDG PET: elevated plasma glucose reduces both uptake and detection rate of pancreatic malignancies. J Nucl Med. 1998;39(6):1030–3.

Part VI
Perioperative Care

Chapter 37
Prehabilitation for Pancreatic Cancer Surgery

Michael Hughes and Kristoffer Lassen

Take Home Messages
- Short term benefits of prehabilitation have been shown in major abdominal surgery
- Evidence for prehabilitation prior to pancreatic surgery is limited
- Pancreatic cancer is associated with cachexia and sarcopenia which could be targeted by prehabilitation programmes

Pearls and Pitfalls
- The benefits of prehabilitation in pancreas surgery are not clearly shown
- Mortality rates are not affected
- Optimum programme not established
- Patients undergoing pancreas surgery often have risk factors that are modifiable
- They have significant nutritional compromise
- Morbidity rates remain high
- These patients could benefit the most from prehabilitation programmes aimed at improving nutritional status as well as cardiorespiratory function

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Further Perspectives
- Precise benefit in pancreatic cancer surgery needs to be shown
- Optimum prehabilitation protocol needs to be established
- Alternative, patient focused outcome measures need to be considered
- Effect of prehabilitation on survival in pancreatic cancer requires investigation
- RCTs required to determine protocol efficacy

37.1 Introduction

Major abdominal surgery initiates a systemic inflammatory response, generalised catabolism and an overall energy deficit. As a result of this recipients of major surgery are at risk of malnutrition, muscle wasting and, ultimately, immune compromise resulting in a reduced ability to recover satisfactorily after surgery [1].

Enhanced Recovery After Surgery (ERAS) has revolutionized perioperative care over the past 25 years with emphasis on early post-operative feeding, mobilization and pain control to mitigate against the effects of the inflammatory response, with resultant improvements in recovery time as well as morbidity rates after major abdominal surgery [2].

Prehabilitation is a concept that has since developed with a focus on optimizing a patient's overall condition prior to surgery. Poorer post-operative outcomes have been reported in patients undergoing surgery with reduced skeletal muscle mass and poor respiratory reserve [3, 4]. The concept of prehabilitation aims to mitigate against this by implementing pre-operative interventions to improve overall cardio-respiratory function and nutritional status.

Initial work investigating efficacy of prehabilitation programmes in the specialties of thoracic and abdominal surgery [5, 6] showed improvements in post-operative short term outcomes when patients underwent pre-operative aerobic conditioning and strength training in order to improve patients' overall condition and functioning before undergoing major surgery. Prehabilitation has also been postulated to have the potential to improve more long-term outcomes such as functional capacity and independence post discharge in the frail patient [7]. The practice of prehabilitation has subsequently been increasingly utilized and investigated in an attempt to optimize outcomes post operatively. It is not yet, however, considered standard of care in the same way that ERAS has become.

37.2 Defining a Prehabilitation Programme

The principles of a prehabilitation programme are for patients to undertake a period of pre-operative optimization of their overall condition and address the significant risk factors. Mainly this has taken the form of physical cardio-respiratory conditioning and nutritional optimization (Fig. 37.1).

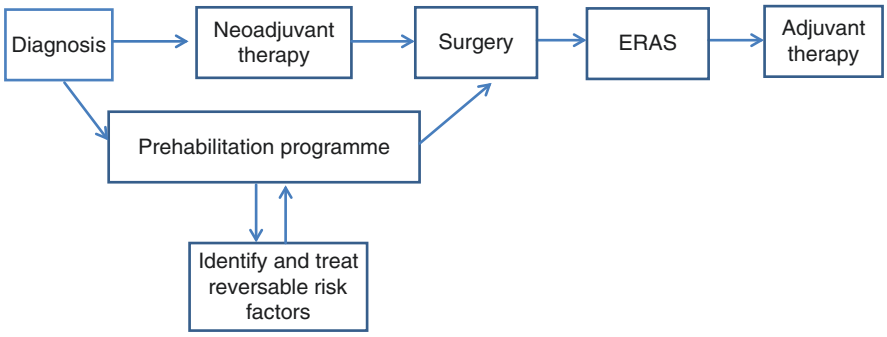

Fig. 37.1 Patient pathway from diagnosis incorporating prehabilitation programme

Physical conditioning is achieved by aerobic exercises such as walking or cycling, normally performed regularly with an increasing level of intensity advised over a prescribed period of time. Other physical exercises include weighted training to increase skeletal muscle mass as well as inspiratory muscle training to improve pulmonary function [8].

The exercises are performed at regular intervals and for a specified length of time pre-operatively. Training can either be supervised, usually by a physiotherapist, or guided but without direct supervision. A typical prehabilitation exercise programme would involve aerobic and resistance exercises once per day for 2–4 weeks before surgery. This could include timed cycling with increasing resistance or walks/jogs of increasing distance and pace [8].

An initial pre-operative intervention undertaken by prehabilitation programmes was pulmonary physiotherapy for patients undergoing cardio-thoracic surgery. This was often in the form of inspiratory muscle training (IMT). This consists of using a resistance device and inhaling and exhaling with varying degrees of force with an aim of increasing the strength and capacity of the inspiratory muscles with the aim of increasing inspiratory muscle mass and overall respiratory function [9].

Similarly nutritional prehabilitation involves an assessment of overall nutritional status, formation of a diet plan and nutritional supplementation, often led by the dietician team for a period of several weeks before surgery. This must aim to provide sufficient proteins to compensate for increased demands during exercise.

The practical methods of conducting prehabilitation programmes vary between protocols. Reported lengths of programmes range from 1 to 6 weeks pre-operatively. Supervision levels, intensity goals, incorporation of nutritional supplementation and the nature of physical conditioning all vary considerably [10]. Furthermore, the location of the physical exercises being undertaken varies from patient homes, community centres to in patient physiotherapy departments. This current heterogeneity potentially reflects the lack of a consistently proven optimum method.

37.3 Potential Benefits of Prehabilitation

Once a prehabilitation programme has been implemented it is critical, both clinically and for research purposes, to establish if the intervention is effective and whether it translates into clinical benefit to the patient. The impact of early trials has been limited by the lack of universally accepted outcomes illustrating the benefit or otherwise of the prehabilitation intervention. Therefore, the question remains as to how the efficacy of prehabilitation programmes should be measured and, of the evidence that is available, what efficacy has been shown.

The six-minute walking test (6 MWT) has been used to assess patients during the prehabilitation period. This is the distance that can be achieved during 6 minutes of walking. This simple test is a validated measure of overall physical functioning and physiological reserve [11]. Prehabilitation programmes have not, however, been shown consistently to improve this outcome measure [12].

Formal cardio-pulmonary exercise testing (CPET) is a further measure of the efficacy of prehabilitation programmes on improving physiological reserve. CPET, which can measure the level at which the anaerobic threshold is achieved during exercise, which in turn is a marker of overall cardiopulmonary conditioning, has been shown consistently to be associated with post-operative outcome [13]. Low anaerobic threshold levels are associated with increased morbidity and length of stay following major surgery [4, 13]. Prehabilitation programmes have also been shown to improve anaerobic threshold levels of patients enrolled in neoadjuvant chemotherapy when compared to controls [14].

37.3.1 Measuring Outcomes in Prehabilitation

However the critical factor is the ability of a prehabilitation programme not only to provide objective benefit of physiological improvement but also to translate this into clinical benefit, most often measured in terms of morbidity, mortality, length of stay and preservation of long-term functional capacity and independence.

When looking specifically at abdominal surgery, prehabilitation has been shown by two meta-analyses to have a beneficial effect in both overall and pulmonary specific morbidity [12, 15]. Length of stay has not been shown to be shortened by prehabilitation protocols in these two analyses of the most recent RCTS in abdominal surgery, which may be as a result of the heterogeneity of included operations and also the variability in post-operative recovery pathways and discharge criteria utilized.

IMT has been shown to be effective in improving respiratory parameters including forced expiratory volume (FEV1) and maximal inspiratory pressure [16–18] as well as rates of post-operative pulmonary morbidity and post-operative length of stay [19] in patients undergoing thoracic and abdominal surgery.

It is important to emphasise that in the available literature, there is considerable variation in the individual prehabilitation protocols utilized [10] with no consensus as to make up or timings of the programmes. This is also true of the control groups in these studies with the comparator varying from no intervention to a "usual care" which includes less intense physical therapy or reduced supervision in comparison to the intervention group, which may explain some of the heterogeneity found in the outcomes of the meta-analyses. However, despite this issue, morbidity, in particular pulmonary morbidity is consistently reported to be reduced after major abdominal surgery by the implementation of prehabilitation measures.

37.4 Prehabilitation Implemented for Pancreatic Surgery

To date prehabilitation programmes have been investigated infrequently in patients undergoing surgery for pancreatic cancer with only one randomised controlled trial (Table 37.1). Patients with pancreatic cancer represent a population that have certain significant characteristics that separate them from the majority of patients undergoing other types of major abdominal surgery and require individual attention.

Pancreatic surgery is often undertaken in patients who have often been recently treated in hospital for a period of time in the pre-operative stage with jaundice, infection and/or malnutrition. The pre-operative work up for patients undergoing pancreatic surgery may therefore present inherent challenges. Obstructive jaundice, with or without infection, may result in emergency admission to hospital (up to 50% of head of pancreas lesions in one study [20]) with subsequent deterioration in

Table 37.1 Prehabilitation trials in pancreas surgery

	Type of study	Prehab programme	Morbidity	LOS	Mortality
Ausania et al. [36]	RCT	Supervised and unsupervised exercises, nutritional, endocrine and exocrine support	ND Less DGE in prehab group	ND	ND
Nakajima et al. [42]	Non randomised retrospective controlled study[a]	60 min exercise 3× per week Nutritional supplement	ND	Reduced in prehab group	ND
Kitahata et al. [25]	Non randomised retrospective controlled study	Individual exercise programme and breathing exercises with in patient prehabilitation plus ERAS protocol post-operatively	ND Reduced pulmonary morbidity in prehab group	Reduced in prehab group	ND

RCT randomised controlled trial, *ND* no difference, *DGE* delayed gastric emptying
[a]Hepatic resections included also

overall conditioning as a result of hospital admission, concurrent infection and nutritional deficit associated with acute illness.

Post-operative morbidity rates after pancreas surgery, particularly after pancreatoduodenectomy for lesions in the head of the pancreas, are notoriously high. Despite significant advances in peri- and post-operative care, and a reduction in mortality rates to below 5%, overall morbidity rates are consistently reported at 40–50% [21]. As such, every effort should be made to minimize this burden. This patient population is potentially one that may have most to benefit from attempts to optimize their pre-operative condition.

Tzeng et al. [22] investigated patients undergoing pancreatoduodenectomy with poor functional status. This group of patients have previously been categorised as "borderline resectable type C" which is a grading system devised by the MD Anderson group that specifically recognises those patients where performance status is the major factor precluding surgical intervention for pancreatic cancer [23]. It was found that 37% of all patients undergoing pancreatoduodenectomy were classified as high risk due to age, comorbidities or conditioning. This group of patients were more at risk of major morbidity and also mortality in general and significantly more at risk of dying if they suffered a major morbidity. It was also noted that the majority of risk factors for developing major morbidity/death in this group were potentially modifiable (dyspnoea, pre-operative sepsis, lack of independent function, ASA 4, transfusion intra-operatively of four or more units.) This therefore raises the question of a considerable need and potential benefit for targeting this patient group with pre-operative optimisation and minimisation of such risk factors. The potential gain for the prehabilitation programmes to target these areas is therefore considerable.

In pancreas surgery, the ability to rescue patients who have developed major morbidity and avoid failure-to-rescue not only rests with the clinical team, but also the underlying condition of the patients [24]. As described above, should a patient have the reversible factors associated with poor outcome then the ability to rescue this group of patients once a major morbidity has occurred is significantly compromised. Prehabilitation, namely optimisation of pre-operative function, cardiorespiratory fitness and skeletal muscle mass, is critical in this group of patients where a complicated post-operative course must be mitigated against as much as possible, especially in patients who are most vulnerable to the impact of major morbidity.

37.5 Perioperative Rehabilitation

Kitahata et al. [25] compared a "perioperative rehabilitation" cohort which included pre-operative exercise training as well as a 1 week hospital admission for pre-operative supervised exercise with their ERAS programme. This was compared with an historical control group that did not receive either of these. There was a

significant reduction in pulmonary morbidity and LOS as well as non prehabilitation being predictive of pulmonary morbidity following multivariable analysis. No difference in postoperative overall morbidity or mortality was observed between the groups. This therefore suggests that prehabilitation is possible in patients undergoing pancreatic surgery with the resulting benefit in reduction in pulmonary morbidity, which is a consistent theme amongst prehabilitation studies. However the use of historical control is a weak methodology in a complex intervention like perioperative optimization and the heterogeneity of the post-operative care limits the impact of its findings.

In non-randomised trials, particularly in pancreatic surgery, high risk patients may not be selected to undergo curative resection on the basis of comorbidities in the context of high-risk surgery. When compared to other forms of abdominal surgery, patient cohorts undergoing pancreatoduodenectomy may therefore comprise relatively fitter patients. The question that requires an answer is what effect can prehabilitation have on frail patients and can it have an effect on functional independence post discharge as well as the proportion of patients being deemed fit for surgery?

37.6 Specific Factors Associated with Pancreatic Surgery to Consider for Prehabilitation

37.6.1 Nutrition and Pancreatic Surgery

Compared with other cancers, pancreatic cancer exerts a significant cachectic effect [26] with 70–80% being cachectic at time of diagnosis [27, 28]. (Cachexia defined as unintended weight loss of greater than 5% in 6 months [29].) It has been reported that 39% of patients with pancreatic cancer will have lost greater than 10% of their body weight prior to diagnosis [30]. Sarcopenia, defined as the generalised and progressive loss of muscle mass and quality [31] has been reported at rates of up to 65% in patients with pancreatic cancer [28]. This may be due to multifactorial reasons, such as the cancer symptoms of pain and anorexia [32]; gastric outlet obstructive symptoms as well as the catabolic effect of pancreatic cancer [26].

Patients undergoing pancreas surgery are also susceptible to specific nutritional requirements, namely pancreatic endocrine and/or exocrine compromises [33]. Development of diabetes either pre or post operatively can compromise nutritional status and overall operative risk and up to 80% of patients with pancreatic cancer present with new onset diabetes [34]. Similarly the development of exocrine dysfunction, which has been reported in up to two third of patients with pancreatic cancer [35] will inevitably affect absorption and requires vigilance in order to prevent such a problem exacerbating an underlying nutritional deficit.

37.6.2 Prehabilitation Tailored to Patients Undergoing Pancreatic Surgery

Prehabilitation programmes developed for pancreas surgery specifically will be mandated to address these potential problems associated with pancreas cancer and surgery. Previous general abdominal surgery prehabilitation programmes have not had to address these issues specifically and so this represents a unique concern.

The only randomized controlled trial that has been performed to date comparing prehabilitation in patients undergoing pancreatoduodenectomy with a control group undergoing standard care [36] addressed this issue. Their programme incorporated endocrine and exocrine function optimization and also one week of supervised cardiovascular training, unsupervised training as well as nutritional optimization, related to individualised needs as determined by a pre-operative multi-disciplinary investigation. The control group was partially prehabilitated. This trial did not, however, show a difference in overall morbidity for Whipple's patients who underwent the prehabilitation programme although there was a significant reduction in rates of delayed gastric emptying in the prehabilitation group. The reasons for this are unclear although may have been related to the (non significant) reduction in pancreatic fistula in the intervention group also. The control group received exercise recommendations as well as smoking cessation and pancreatic enzyme supplementation. This, common with other prehabilitation studies, may explain the lack of observed effect.

The effect of sarcopenia on perioperative outcomes has been investigated in patients undergoing pancreatic surgery. There is meta-analysis evidence of poorer short term outcomes post pancreatic surgery for patients with sarcopenia, most notably length of stay [37]. Although this has not been shown consistently and the evaluation method of sarcopenia is often cited as contributory to variability in findings [38]. What has been shown more consistently is the relationship between sarcopenia in patients with pancreatic surgery and disease free and overall survival with the presence of sarcopenia being a poor prognostic indicator for patients with pancreatic cancer [39] and those undergoing surgery [40].

37.6.3 Preoperative Exercise and Pancreatic Surgery

The benefit of exercise, both aerobic, resistance training and a combination of the two have been shown to have a therapeutic benefit in populations with sarcopenia, albeit not with cancer related sarcopenia. Nevertheless the mechanisms of sarcopenia have been investigated on animal models with mitigation against these being demonstrated with the intervention of exercise [41].

Nakajima et al. [42] compared prehabilitation with a historical control group in patients undergoing pancreatoduodenectomy as well as major hepatic resections. Their prehabilitation programme involved unsupervised cardiopulmonary exercises

and resistance training of one hour, three times per week as well as essential amino acid supplementation taken after exercise. There was no difference in overall morbidity rates, but there was a decrease in length of stay in the prehabilitation group. Also nutritional assessments performed showed improved albumin and decreased weight loss before surgery in the prehabilitation group, as well as improvements in 6 MWT distance. This suggests that patients with pancreatic cancer are able to respond to nutritional interventions in an attempt to negate the cachectic effects of pancreatic cancer prior to surgery.

37.6.4 Timing of Prehabilitation in Pancreatic Surgery

Patients scheduled for pancreatic surgery will generally fall into two groups. Some will be scheduled for direct surgery while others will need a stenting procedure or undergo a course of neoadjuvant chemotherapy. Both situations pose challenges for a prehabilitation programme. Where upfront surgery is recommended the time available for prehabilitation will be defined by the logistics and capacity of the surgical department. Even in the absence of other constraints, it is the authors' experience that few departments will be able to offer a pancreatoduodenectomy without a delay of 2–3 weeks as routine. Hence, provided that a prehabilitation program is initiated immediately following diagnosis, there should be sufficient time for a meaningful intervention. In selected cases of increased risk, it may well be prudent to delay surgery for another week or two to ensure a benefit from prehabilitation and optimization.

However, increasingly, patients with PDAC are undergoing neoadjuvant chemotherapy prior to exploratory or resectional surgery [43]. This builds in a predictable period of time before surgery when a period of prehabilitation could potentially be implemented. This is not currently routine practice and not all patients undergoing pancreatic surgery will be receiving treatment for PDAC. However, if an increasing proportion of patients undergoing pancreatic surgery will receive neoadjuvant treatment, then this provides an opportunity to attempt physical and nutritional optimisation, particularly in the context of having received chemotherapy with associated threats to functional capacity.

The issue of whether patients undergoing neoadjuvant chemotherapy are able to undergo exercise programmes was addressed by Parker et al. [44] Patients with pancreatic malignancy were prescribed up to 120 min of exercises per week as part of a home based, self-reported exercise regimen. The included patients were able to undertake such a programme with higher levels of reported exercise than prescribed. This therefore represents feasibility of potential prehabilitation programmes in patients with pancreatic cancer undergoing neoadjuvant chemotherapy prior to surgery. Within this small study there were noted to be issues with adherence variability. Therefore, it may be that challenges remain in this population, however this provides a basis on which to attempt implementation.

Furthermore, it has been demonstrated that patients undergoing urgent diagnostic investigation for suspected cancer are able to undergo community-based detection and optimisation of risk factors prior to surgery without interference with the diagnostic work up [45].

Adjuvant chemotherapy following surgery for pancreatic ductal adenocarcinoma is considered standard of care. Significant proportions of patients, however, do not go on to receive chemotherapy following a complicated post-operative course. Patients affected by major post-operative morbidity or elderly patients often do not receive adjuvant chemotherapy due to ongoing frailty, up to 50% in one report [46]. This is a potential area that prehabilitation could be employed in an effort to mitigate against this disruption to cancer treatment.

37.7 Areas for Future Research

The optimum outcome measure to judge the benefit of prehabilitation has not been determined yet. The current literature focuses mainly on objective physiological measures and short term post-operative outcomes. A patient focused approach should also prioritize alternative outcome measures. Particularly when considering pancreatic surgery, high proportions of patients are medically high risk [22] and may be deemed unsuitable for surgery. Furthermore, frail and elderly patients undergoing surgery are often unable to return to functional independence post-operatively [47] or receive adjuvant chemotherapy. Future research should focus on outcome measures such as these, namely can a prehabilitative programme improve the proportions of frail patients undergoing curative surgery, being discharged with a satisfactory level of function or able to regain such a level and being fit enough to go onto adjuvant chemotherapy if appropriate. This approach would ensure that the effects of prehabilitation could be assessed in practical, patient centred terms.

There is a great deal of heterogeneity when looking at the current prehabilitation programmes for major abdominal surgery and pancreatic surgery. Both in terms of the make up of the programme, i.e. included components such as weight training, aerobic training, timings, length of sessions and also the level of supervision. There is also inconsistency in the current literature regarding the control group that the prehabilitation groups are compared to. This often leads to inability to interpret meta-analyses accurately. The difficulty can arise when the intuitive benefits of a programme are suspected and the disinclination to “deprive” the control group of at least some of the benefits of the intervention group. Such practice is entirely understandable and, it may be that prehabilitation versus no prehabilitation should no longer be the focus of the research question, and that the precise make-up of the prehabilitation programme needs to be formalized. This is particularly important for prehabilitation programmes addressing pancreatic surgery as there are several components that are particularly pertinent to this population, namely the high risk of cachexia and skeletal muscle loss, the potential deconditioning due to jaundice and infection and also the potential requirements for endocrine and exocrine

supplementation. In any case despite the absence of consistent protocols guiding intervention, no prehabilitation programme may be an inappropriate course of action in light of consistent feasibility and safety being reported.

37.8 Conclusions

Prehabilitation programmes have been shown to provide benefit in terms of improvement in post-operative morbidity in the fields of major abdominal surgery. The evidence for its benefit in surgery for pancreatic disease is limited at present. However, pancreatic malignancy and surgery present many unique challenges that coincide with the priorities of current prehabilitation programmes. As the use of prehabilitation increases evidence will come to allow objective analysis of the benefits that they may provide. Further procedure specific studies are required to address this, however, care must be taken in determining the constituent of the control arm to ensure standard of care is addressed. On the basis of the available data however, mainly from non-pancreatic abdominal surgery, the encouragement of aerobic and resistance exercises, ideally supervised by the physiotherapy department prior to surgery, as well as awareness of potential nutritional deficiencies to be addressed would be appropriate whilst ongoing trials continue to report procedure specific results on revised protocols.

References

1. Dabrowska AM, Slotwinski R. The immune response to surgery and infection. Cent Eur J Immunol. 2014;39(4):532–7.
2. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg. 2017;152(3):292–8.
3. Amini N, et al. Impact total psoas volume on short- and long-term outcomes in patients undergoing curative resection for pancreatic adenocarcinoma: a new tool to assess sarcopenia. J Gastrointest Surg. 2015;19(9):1593–602.
4. Lai CW, et al. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. Br J Anaesth. 2013;111(4):607–11.
5. Mans CM, Reeve JC, Elkins MR. Postoperative outcomes following preoperative inspiratory muscle training in patients undergoing cardiothoracic or upper abdominal surgery: a systematic review and meta analysis. Clin Rehabil. 2015;29(5):426–38.
6. Valkenet K, et al. The effects of preoperative exercise therapy on postoperative outcome: a systematic review. Clin Rehabil. 2011;25(2):99–111.
7. Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? Anaesthesia. 2019;74(Suppl 1):20–6.
8. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care. 2005;8(1):23–32.
9. Hulzebos EH, et al. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006;296(15):1851–7.

10. Kamarajah SK, et al. Critical appraisal on the impact of preoperative rehabilitation and outcomes after major abdominal and cardiothoracic surgery: a systematic review and meta-analysis. Surgery. 2020;167:540.
11. Chen YC, et al. Validating the 6-minute walk test as an indicator of recovery in patients undergoing cardiac surgery: a prospective cohort study. Medicine (Baltimore). 2018;97(42):e12925.
12. Hughes MJ, et al. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg. 2019;43(7):1661–8.
13. West MA, et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2014;112(4):665–71.
14. West MA, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth. 2015;114(2):244–51.
15. Moran J, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. Surgery. 2016;160(5):1189–201.
16. Kulkarni SR, et al. Pre-operative inspiratory muscle training preserves postoperative inspiratory muscle strength following major abdominal surgery - a randomised pilot study. Ann R Coll Surg Engl. 2010;92(8):700–7.
17. Barbalho-Moulim MC, et al. Effects of preoperative inspiratory muscle training in obese women undergoing open bariatric surgery: respiratory muscle strength, lung volumes, and diaphragmatic excursion. Clinics (Sao Paulo). 2011;66(10):1721–7.
18. Llorens J, et al. Preoperative inspiratory muscular training to prevent postoperative hypoxemia in morbidly obese patients undergoing laparoscopic bariatric surgery. A randomized clinical trial. Obes Surg. 2015;25(6):1003–9.
19. Kendall F, et al. Inspiratory muscle training is effective to reduce postoperative pulmonary complications and length of hospital stay: a systematic review and meta-analysis. Disabil Rehabil. 2018;40(8):864–82.
20. Elliss-Brookes L, et al. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. Br J Cancer. 2012;107(8):1220–6.
21. Kimura W, et al. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. Ann Surg. 2014;259(4):773–80.
22. Tzeng CW, et al. Morbidity and mortality after pancreaticoduodenectomy in patients with borderline resectable type C clinical classification. J Gastrointest Surg. 2014;18(1):146–55; discussion 155–6.
23. Katz MH, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206(5):833–46; discussion 846–8.
24. Gleeson EM, et al. Patient-specific predictors of failure to rescue after pancreaticoduodenectomy. HPB (Oxford). 2019;21(3):283–90.
25. Kitahata Y, et al. Intensive perioperative rehabilitation improves surgical outcomes after pancreaticoduodenectomy. Langenbeck's Arch Surg. 2018;403(6):711–8.
26. Tan CR, et al. Pancreatic cancer cachexia: a review of mechanisms and therapeutics. Front Physiol. 2014;5:88.
27. Wigmore SJ, et al. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer. 1997;75(1):106–9.
28. Ozola Zalite I, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology. 2015;15(1):19–24.
29. Fearon K, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
30. Nemer L, et al. Predictors of pancreatic cancer-associated weight loss and nutritional interventions. Pancreas. 2017;46(9):1152–7.
31. Cruz-Jentoft AJ, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412–23.

32. Holly EA, et al. Signs and symptoms of pancreatic cancer: a population-based case-control study in the San Francisco Bay area. Clin Gastroenterol Hepatol. 2004;2(6):510–7.
33. Bartel MJ, et al. Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. Dig Liver Dis. 2015;47(12):1013–20.
34. Bartosch-Harlid A, Andersson R. Diabetes mellitus in pancreatic cancer and the need for diagnosis of asymptomatic disease. Pancreatology. 2010;10(4):423–8.
35. Sikkens EC, et al. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol. 2014;48(5):e43–6.
36. Ausania F, et al. Prehabilitation in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. Rev Esp Enferm Dig. 2019;111(8):603–8.
37. Ratnayake CB, et al. Impact of preoperative sarcopenia on postoperative outcomes following pancreatic resection: a systematic review and meta-analysis. Pancreatology. 2018;18(8):996–1004.
38. Chan MY, Chok KSH. Sarcopenia in pancreatic cancer - effects on surgical outcomes and chemotherapy. World J Gastrointest Oncol. 2019;11(7):527–37.
39. Tan BH, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973–9.
40. Mintziras I, et al. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: systematic review and meta-analysis. Int J Surg. 2018;59:19–26.
41. Yoo SZ, et al. Role of exercise in age-related sarcopenia. J Exerc Rehabil. 2018;14(4):551–8.
42. Nakajima H, et al. Clinical benefit of preoperative exercise and nutritional therapy for patients undergoing hepato-pancreato-biliary surgeries for malignancy. Ann Surg Oncol. 2019;26(1):264–72.
43. Klaiber U, et al. Neoadjuvant and adjuvant chemotherapy in pancreatic cancer. Langenbeck's Arch Surg. 2018;403(8):917–32.
44. Parker NH, et al. Physical activity and exercise during preoperative pancreatic cancer treatment. Support Care Cancer. 2019;27(6):2275–84.
45. Barlow RC, et al. Fit for cancer treatment: a prospective feasibility study of primary care initiated prehabilitation for patients with suspected cancer. BJGP Open. 2018;2(4):bjgpopen18X101608.
46. Bakens MJ, et al. The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis. Cancer Med. 2016;5(10):2825–31.
47. Lawrence VA, et al. Functional independence after major abdominal surgery in the elderly. J Am Coll Surg. 2004;199(5):762–72.

Chapter 38
Enhanced Recovery Principles in Pancreatic Cancer Surgery

Emmanuel Melloul and Nicolas Demartines

Take Home Messages

- High compliance (>70%) to ERAS protocol improves outcomes after pancreatoduodenectomy
- Pancreatoduodenectomy should be performed without prior endoscopic stenting for asymptomatic patients with bilirubin level below 250 μmol/L
- Preoperative nutritional assessment expanding beyond calculation of BMI and weight-loss based on self-reported pre-morbid weight and weight scaling upon admission is not warranted before pancreatoduodenectomy
- Preoperative nutritional intervention is recommended for pancreatic cancer patients with severe weight-loss; however, not as a general measure (i.e. >15% weight-loss or BMI < 18.5 kg/m^2)

Pearls and Pitfalls

- Strict adhesion to the proposed ERAS protocol with regular internal audit are paramount for the successful implementation of ERAS in pancreatoduodenectomy
- Results of the implementation of ERAS in pancreatic surgery are conflicting but the majority of studies did not comply with all the 26 items of the proposed protocol

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Future Perspectives

- A well-established and standardized ERAS protocol is paramount for evidence-based management of patients.
- Compliance with the ERAS protocol should be documented with standardized database and interactive audit system to follow the real actual application of the protocol and outcomes

38.1 Introduction

Enhanced recovery after surgery (ERAS) is a multimodal pathway that has been widely introduced to reduce the surgical stress and improve recovery after major surgery. It is validated in many types of surgery since it reduces postoperative medical complications, hospital stay and costs [1–3]. A recent meta-analysis confirmed the positive impact of ERAS on postoperative recovery after pancreatoduodenectomy [4]. The first ERAS guidelines for pancreatoduodenectomy included 26 items and were published in 2012 [5]. These guidelines have been updated in 2019 and are displayed with their respective level of evidence and grading in Table 38.1.

Table 38.1 Summary of updated ERAS recommendations for pancreatoduodenectomy for each items and their respective level of evidence and grade

ERAS item	Recommended (YES/NO)	Evidence level	Grade of recommendation
1. Preoperative counselling	YES	Moderate	Weak
2. Prehabilitation	YES	Moderate	Strong
3. Preoperative biliary drainage	NO unless decompression is needed (bilirubin level above 250 µmol/L, preoperative episodes of cholangitis, neoadjuvant treatment).	High	Strong
4. Avoiding Preoperative smoking and alcohol consumption	YES	Smoking cessation: Moderate; Alcohol cessation for moderate users: Low	Strong
		Alcohol cessation for high users: High	
5. Preoperative nutrition	YES for patients with severe weight-loss (i.e. >15% weight-loss or BMI < 18.5 kg/m^2 secondary to their disease).	>15% weight loss: High	Strong
6. Perioperative oral immunonutrition	NO	High	Strong

Table 38.1 (continued)

ERAS item	Recommended (YES/NO)	Evidence level	Grade of recommendation
7. Preoperative fasting and treatment with carbohydrates	Preoperative fasting: limited to 6 h for solids and 2 h for liquids in patients without specific risk factors (i.e. gastric outlet obstruction, diabetes with severe neuropathy)	Moderate	Strong
	Carbohydrate loading: NO	Moderate	Strong
8. Pre-anesthetic medication	Pharmacological anxiolytics: NO	Moderate	Strong
	Opioid sparing multimodal pre-anaesthetic medication: YES	Moderate	Strong
	NSAIDS or selective COX2 inhibitor (good renal function): YES	Moderate	Strong
9. Anti-thrombotic prophylaxis	YES	High	Strong
	Mechanical measures: YES	Low	Weak
10. Antimicrobial prophylaxis (less than 60 min before incision) and Alcohol based skin preparation	Single dose intravenous antibiotics: YES	High	Strong
	Alcohol based preparations: YES	Moderate	Strong
11. Epidural analgesia	YES	Moderate	Strong
12. Postoperative intravenous and per oral analgesia	YES	Moderate	Strong
13. Wound catheter and transversus abdominis plane (TAP) block as an alternative to Epidural	YES	High	Strong
14. Postoperative nausea and vomiting (PONV) prophylaxis	YES	Moderate	Strong
15. Avoiding hypothermia (above 36 °C)	YES	High	Strong
16. Postoperative glycaemic control	YES	Moderate	Strong

(continued)

Table 38.1 (continued)

ERAS item	Recommended (YES/NO)	Evidence level	Grade of recommendation
17. Maintenance of Nasogastric intubation	NO	Moderate	Strong
18. Fluid balance (avoidance of fluid overload)	YES	Moderate	Strong
19. Early drain removal at 72 h in patients with an amylase content in drain <5000 U/L on POD1	YES	Selective no-drain regimen: Moderate	Selective no-drain regimen: Weak
		Early removal: High	Early removal: Strong
20. Somatostatin analogues	NO	Moderate	Weak
21. Urinary catheter removal at day 1	In patients with wound catheters or intravenous analgesia: YES	Low	Strong
	All others: NO		
22. Strategies to prevent Delayed gastric emptying	None	Low	Strong
23. Stimulation of bowel movement	Chewing gum: YES	Moderate	Weak
	Alvimopan: YES	Moderate	Weak
	Mosapride: YES	Very low	Weak
	Metoclopramide: NO	Very low	Weak
	Other drugs (Ghrelin receptor antagonists, dihydroergotamine and neostigmine, Erythromycin): NO	Very low (Ghrelin receptor antagonists, dihydroergotamine and neostigmine)	Weak (Ghrelin receptor antagonists, dihydroergotamine and neostigmine)
		Moderate (Erythromycin)	Strong (Erythromycin)
24. Postoperative normal diet and artificial nutrition	Normal diet: YES	Moderate	Strong
	Artificial nutrition as an individual approach according to nutritional status assessment (enteral route preferred): YES		
25. Early and scheduled mobilization	YES	Low	Strong
26. Laparoscopic and Robotic surgery	Laparoscopic surgery: YES	Moderate	Strong
	Robotic surgery: NO	Low	Weak
27. Audit	YES	Moderate	Strong

Adapted from Melloul E. et al. [6]

Cancer patients are more prone to malnutrition, weight loss, and reduction in the physical performance status. These factors impact directly on short and long-term surgical outcome. The ESPAC-3 trial showed that the most important factor for long-term survival in pancreas adenocarcinoma is to achieve complete cycles (at least 6 cycles) of adjuvant chemotherapy. However, if it is not possible to undergo full cycles, it is better to wait for a full post-operative recovery than to start early without being able to finish the treatment [7]. On the other hand, delayed chemotherapy after 12 weeks is not associated with a decreased long-term survival for pancreatic cancer, because adjuvant chemotherapy is a prognostic factor by itself, so it should be offered even lately [8]. It is then paramount that pancreatic cancer patients who underwent surgery are fit enough to complete all full cycles of adjuvant chemotherapy.

This chapter will focus on ERAS items that need particular consideration in pancreatic cancer patients.

38.2 Preoperative Biliary Drainage

The majority of patients with pancreatic head cancer present with jaundice at the time of diagnosis. Complication related to preoperative biliary stenting have been assessed in 12 meta-analyses [9–20]. Preoperative drainage is associated with increased postoperative complications, including wound complications, but without impact on mortality [10–13, 15, 17, 18, 20]. These results are confirmed by a review of the National Surgical Quality Improvement Program (NSQIP) database, which found increased risk of sepsis and wound infections after drainage without impact on mortality [21]. One of the meta-analysis did not demonstrate any postoperative adverse effects after drainage [9]. Moreover, one single meta-analysis showed less major adverse effects with preoperative biliary drainage [16].

According to the last Cochrane reviews on this topic from 2012 (including four RCTs focused on percutaneous transhepatic biliary drainage and two on endoscopic stenting), there was no difference in postoperative mortality, but morbidity rates were higher in pre-operative biliary drainage [19]. Analyzing 1500 pancreatoduodenectomies, the Verona group observed neither increased major complications nor mortality after biliary drainage, but higher surgical site infection rates (SSI) [22].

Resection should be performed without prior endoscopic stenting for asymptomatic patients with bilirubin level below 250 μmol/L [23]. In a multicentric study, serum bilirubin level ≥300 μmol/L increased severe morbidity and decreased long-term survival after PD for pancreatic ductal adenocarcinoma (PDAC) [24]. These findings suggest that biliary stenting is recommended before pancreatoduodenectomy in patients with PDAC and severe jaundice (bilirubin level above 250 μmol/L), even if asymptomatic.

38.3 Preoperative Nutrition

The majority of patients with pancreatic malignancy have significant weight loss before surgery [25]. Based on pre-disease self-reported weight, 5% weight-loss has been demonstrated to be a significant predictor of complications [26]. This emphasize the need for supplemental nutrition, trying to restore baseline nutritional status prior to complex operations, such as a Whipple procedure.

Nutritional interventions (parenteral, enteral or oral/sip-feeds) are recommended for patients with significant weight-loss planned for major operations and these interventions will usually result in weight gain [27, 28]. It remains unproven that preoperative nutritional support reduces complication rates or enhances recovery [29]. A recent evaluation of several established screening tools for malnutrition demonstrated the absence of prognostic power in pancreatic surgery [30].

Nutritional support is recommended for patients with weight-loss >15% or BMI-drop to <18.5 kg/m^2 [31]. For patients with moderate weight-loss, preoperative nutrition support is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines from 2006 to 2017, but this is based on uncontrolled or un-blinded trials, or using surrogate endpoints [27, 28]. Of 35 randomized controlled trials included in latest ESPEN recommendation of 2017, none were published later than 2004 [28].

To summarize, preoperative nutritional assessment expanding beyond calculation of BMI and weight-loss based on self-reported pre-morbid weight and weight scaling upon admission is not warranted. Preoperative nutritional intervention is recommended for patients with severe weight-loss; however, not as a general measure (i.e. >15% weight-loss or BMI $\leq$ 18.5 kg/m^2).

38.4 Perioperative Oral Immunonutrition

Pancreatic cancer patients tend to have high levels of pro-inflammatory cytokines as well as malnutrition and cachexia [32–34]. Through its potential to modulate the perioperative inflammatory response, immunonutrition containing arginine, glutamine, $\omega - 3$ fatty acids and nucleotides has been associated in several meta-analyses with decreased complication rates and length of hospital stay after major gastrointestinal cancer surgery [30, 35–39]. However, study heterogeneity was high, and optimal timing for administration debated [40–42]. Specific evidence on immunonutrition in pancreatic surgery is scarce [43]. An RCT including >200 patients did not demonstrate advantage of routine postoperative immunonutrition in elective upper gastrointestinal surgery patients [41]. Three recent RCTs demonstrated a favorable effect of either pre- or perioperative enteral immunonutrition on systemic immunity in patients undergoing pancreatoduodenectomy [44–46].

The potential benefits of different combinations of immunonutrients in major abdominal surgery was evaluated recently [47]. Immunonutrition compared with control groups reduced overall and infectious complications in 83 RCTs with 7116 patients (grade of evidence low to moderate). Of note, these effects vanished after excluding trials at high risk of bias. Non-industry-funded trials did not display positive effects for overall complications, whereas industry-funded reported large effects [40–42]. According to these data immunonutrition is currently not recommended. More non-industry-funded studies are then needed to assess the real indication of immunonutrients in the perioperative period of pancreatic cancer patients.

38.5 Antithrombotic Prophylaxis

Cancer and pancreatic surgery are two independent risk factors for postoperative deep venous thrombosis (DVT) and pulmonary embolism (PE). It concerns a majority of elderly cancer patients at high risk of venous thromboembolism (VTE) with complications [48, 49].

The ASCO guidelines update recommend systematic postoperative thromboprophylaxis up to 4 weeks in oncologic patients undergoing major abdominal surgery with high-risk features [50]. The low molecular weight heparin (LMWH) or unfragmented heparin (UFH) treatment should be started 2–12 h before surgery [49]. A recent Cochrane review reported no difference between perioperative LMWH, UFH and fondaparinux on mortality, VTE outcomes, and bleeding (minor or major). LMWH is preferable because of compliance (once-daily administration) [51]. The additional use of compressive stockings and intermittent pneumatic compression devices is recommended [52].

In a comparative cohort study (n = 186), patients undergoing pancreatoduodenectomy receiving thromboprophylaxis had less postoperative VTE but significantly more postoperative hemorrhages. Minor hemorrhages were significantly increased, while major hemorrhage remained unchanged [53]. A large cohort study (n = 13,771) confirmed that the rate of post pancreatectomy VTE outnumber hemorrhages [54]. Multivariate analysis identified obesity, age >75 years and organ space infection as risk factors for late VTE. Combined perioperative thromboprophylaxis and epidural analgesia is safe if placement or removal of catheter is delayed for at least 12 h after prophylactic LMWH. No additional hemostasis altering medications should be administered because of additive effects. LMWH should resume at least 4 h after catheter removal [55].

To summarize, LMWH or UFH reduces the risk of VTE complications and should be started 2–12 h before surgery and continued until hospital discharge. Extended thromboprophylaxis (4 weeks) is advised after pancreatoduodenectomy for cancer. In addition, mechanical measures are advised in addition to chemical thromboprophylaxis.

38.6 Postoperative Artificial Nutrition

Malnutrition is preponderant among patients with pancreatic cancer, and morbidity rates of up to 40% after major pancreatic surgery including specific complications such as delayed gastric emptying (DGE), estimated between 30% and 40% of patients after Whipple, request thorough identification and timely support of patients at nutritional risk [56–58]. Early normal diet according to tolerance is safe and feasible, according to several RCTs and systematic reviews [59–62], even in the presence of DGE or pancreatic fistula [57, 63]. Therefore, an early normal diet as tolerated should be encouraged. In patients in whom intake of less than 60% of their energy requirements for 7–10 days has to be expected, artificial postoperative nutritional support strategies should be considered [28, 64]. However, the route of administration is debated due to inherent morbidity of either support strategy and ambiguous results of the available literature [65–67]. While some studies showed a beneficial effect of early enteral tube feeding notably due to its potential to maintain gastrointestinal integrity [68–72], either combined parenteral nutrition or total parenteral nutrition have been suggested as alternatives when enteral nutrition was not feasible [73–75]. In frail patients undergoing oncological adjuvant protocols and needing long-term supplementation, feeding through tube jejunostomy may be considered [76, 77]. Considering these principles, an individual approach based on patients' nutritional status, disease presentation and expected postoperative course should guide postoperative support strategies if normal diet at will is not sufficient.

38.7 Minimal Invasive Surgery

Although a recent randomized controlled trial and a meta-analysis addressed the role of ERAS in pancreatic surgery, these studies did not differentiate for outcomes in minimally invasive pancreatic surgery [4, 78].

Three randomized controlled trials compared postoperative outcome after laparoscopic pancreatoduodenectomy to open pancreatoduodenectomy in a total of 229 patients [79–81].

The first study was the single center PLOT RCT from India [80]. This study found a significantly shorter length of stay and significantly less intra operative blood loss [80]. Duration of surgery was however significantly longer in the laparoscopic group.

The second study was the monocenter PADULAP RCT from Spain in 66 patients [79]. This study found a significantly better outcome regarding Clavien grade ≥ 3 complications for the laparoscopic compared to open pancreatoduodenectomy. Both the PLOT and PADULAP studies were single center studies from highly experienced centers. In both studies, sample size were calculated for length of stay as primary outcome and therefore no definitive conclusions can be drawn on the impact of laparoscopic pancreatoduodenectomy on postoperative complications.

The third study was the multicenter LEOPARD-2 RCT from the Netherlands [81]. All patients were treated according to enhanced recovery principles. This study was stopped early after randomization of 99 patients because of safety concerns (increased mortality in laparoscopy group) and found no difference in time to functional recovery [82].

According to the last updated ERAS guidelines for pancreatic surgery, no studies were found assessing patients undergoing robotic assisted pancreatoduodenectomy within an ERAS protocol. A systematic review and meta-analysis found only five non-randomized prospective studies comparing robotic-assisted with open pancreatoduodenectomy [83]. Robotic assisted pancreatoduodenectomy was associated with less blood loss and lower overall complications, but longer operative duration. No significant differences were found in the rates of pancreatic fistula, DGE, and length of hospital stay compared to open pancreatoduodenectomy [83]. Currently, there is insufficient evidence to assess robotic assisted pancreatoduodenectomy. Prospective studies from high volume centers are needed.

38.8 Conclusion

Further data are needed to confirm the impact of ERAS protocol on the long-term oncologic outcome and reduction in the delay to adjuvant chemotherapy for pancreatic cancer. Therefore, a well-established and standardized ERAS protocol is paramount for evidence-based management of patients. Compliance with the ERAS protocol should be documented with standardized database and interactive audit system to follow the real actual application of the protocol and outcomes. In addition, it will become key part of future trials thus allowing benchmarking.

References

1. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: enhanced recovery after surgery (ERAS (R)) society recommendations. Clin Nutr. 2013;32(6):879–87.
2. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Grp ZFTS. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009;136(3):842–7.
3. Roulin D, Donadini A, Gander S, Griesser AC, Blanc C, Hubner M, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. Br J Surg. 2013;100(8):1108–14.
4. Ji HB, Zhu WT, Wei Q, Wang XX, Wang HB, Chen QP. Impact of enhanced recovery after surgery programs on pancreatic surgery: a meta-analysis. World J Gastroenterol. 2018;24(15):1666–78.
5. Lassen K, Coolsen MME, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: enhanced recovery after surgery (ERAS®) Society recommendations. Clin Nutr. 2012;31(6):817–30.

6. Melloul E, Lassen K, Roulin D, Grass F, Perinel J, Adham M, Wellge EB, Kunzler F, Besselink MG, Asbun H, Scott MJ, Dejong CHC, Vrochides D, Aloia T, Izbicki JR, Demartines N. World J Surg. 2020;44(7):2056-084. https://doi.org/10.1007/s00268-020-05462-w.
7. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
8. Mirkin KA, Greenleaf EK, Hollenbeak CS, Wong J. Time to the initiation of adjuvant chemotherapy does not impact survival in patients with resected pancreatic cancer. Cancer. 2016;122(19):2979–87.
9. Saleh MM, Norregaard P, Jorgensen HL, Andersen PK, Matzen P. Preoperative endoscopic stent placement before pancreaticoduodenectomy: a meta-analysis of the effect on morbidity and mortality. Gastrointest Endosc. 2002;56(4):529–34.
10. Sewnath ME, Birjmohun RS, Rauws EA, Huibregtse K, Obertop H, Gouma DJ. The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg. 2001;192(6):726–34.
11. Wang CC, Kao JH. Preoperative drainage in pancreatic cancer. N Engl J Med. 2010;362(14):1343; author reply 5.
12. Velanovich V, Kheibek T, Khan M. Relationship of postoperative complications from preoperative biliary stents after pancreaticoduodenectomy. A new cohort analysis and meta-analysis of modern studies. JOP. 2009;10(1):24–9.
13. Garcea G, Chee W, Ong SL, Maddern GJ. Preoperative biliary drainage for distal obstruction: the case against revisited. Pancreas. 2010;39(2):119–26.
14. Sun C, Yan G, Li Z, Tzeng CM. A meta-analysis of the effect of preoperative biliary stenting on patients with obstructive jaundice. Medicine (Baltimore). 2014;93(26):e189.
15. Chen Y, Ou G, Lian G, Luo H, Huang K, Huang Y. Effect of preoperative biliary drainage on complications following pancreatoduodenectomy: a meta-analysis. Medicine (Baltimore). 2015;94(29):e1199.
16. Moole H, Bechtold M, Puli SR. Efficacy of preoperative biliary drainage in malignant obstructive jaundice: a meta-analysis and systematic review. World J Surg Oncol. 2016;14(1):182.
17. Scheufele F, Schorn S, Demir IE, Sargut M, Tieftrunk E, Calavrezos L, et al. Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head: a meta-analysis of current literature. Surgery. 2017;161(4):939–50.
18. Lee PJ, Podugu A, Wu D, Lee AC, Stevens T, Windsor JA. Preoperative biliary drainage in resectable pancreatic cancer: a systematic review and network meta-analysis. HPB. 2018;20(6):477–86.
19. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, et al. Pre-operative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev. 2012;9:CD005444.
20. Qiu YD, Bai JL, Xu FG, Ding YT. Effect of preoperative biliary drainage on malignant obstructive jaundice: a meta-analysis. World J Gastroenterol. 2011;17(3):391–6.
21. Shaib Y, Rahal MA, Rammal MO, Mailhac A, Tamim H. Preoperative biliary drainage for malignant biliary obstruction: results from a national database. J Hepato Bili Pancreat Sci. 2017;24(11):637–42.
22. De Pastena M, Marchegiani G, Paiella S, Malleo G, Ciprani D, Gasparini C, et al. Impact of preoperative biliary drainage on postoperative outcome after pancreaticoduodenectomy: an analysis of 1500 consecutive cases. Dig Endosc. 2018;30(6):777–84.
23. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129–37.
24. Sauvanet A, Boher JM, Paye F, Bachellier P, Sa Cuhna A, Le Treut YP, et al. Severe jaundice increases early severe morbidity and decreases long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. J Am Coll Surg. 2015;221(2):380–9.
25. Olson SH, Xu Y, Herzog K, Saldia A, DeFilippis EM, Li P, et al. Weight loss, diabetes, fatigue, and depression preceding pancreatic cancer. Pancreas. 2016;45(7):986–91.

26. Aahlin EK, Trano G, Johns N, Horn A, Soreide JA, Fearon KC, et al. Risk factors, complications and survival after upper abdominal surgery: a prospective cohort study. BMC Surg. 2015;15:83.
27. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. Clin Nutr. 2006;25(2):224–44.
28. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
29. Lassen K, Hvarphiye A, Myrmel T. Randomised trials in surgery: the burden of evidence. Rev Recent Clin Trials. 2012;7(3):244–8.
30. Probst P, Haller S, Bruckner T, Ulrich A, Strobel O, Hackert T, et al. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS Pancreas). Br J Surg. 2017;104(8):1053–62.
31. Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018;164(5):1035–48.
32. Poch B, Lotspeich E, Ramadani M, Gansauge S, Beger HG, Gansauge F. Systemic immune dysfunction in pancreatic cancer patients. Langenbeck's Arch Surg. 2007;392(3):353–8.
33. Ashida R, Okamura Y, Wakabayashi-Nakao K, Mizuno T, Aoki S, Uesaka K. The Impact of preoperative enteral nutrition enriched with eicosapentaenoic acid on postoperative hypercytokinemia after pancreatoduodenectomy: the results of a double-blinded randomized controlled trial. Dig Surg. 2019;36:348–56.
34. Senkal M, Haaker R, Linseisen J, Wolfram G, Homann HH, Stehle P. Preoperative oral supplementation with long-chain Ω-3 fatty acids beneficially alters phospholipid fatty acid patterns in liver, gut mucosa, and tumor tissue. J Parenter Enter Nutr. 2005;29(4):236–40.
35. Mazaki T, Ishii Y, Murai I. Immunoenhancing enteral and parenteral nutrition for gastrointestinal surgery: a multiple-treatments meta-analysis. Ann Surg. 2015;261(4):662–9.
36. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg. 2011;212(3):385–99, 99 e1.
37. Osland E, Hossain MB, Khan S, Memon MA. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. JPEN J Parenter Enteral Nutr. 2014;38(1):53–69.
38. Cheng Y, Zhang J, Zhang L, Wu J, Zhan Z. Enteral immunonutrition versus enteral nutrition for gastric cancer patients undergoing a total gastrectomy: a systematic review and meta-analysis. BMC Gastroenterol. 2018;18(1):11.
39. Song GM, Liu XL, Bian W, Wu J, Deng YH, Zhang H, et al. Systematic review with network meta-analysis: comparative efficacy of different enteral immunonutrition formulas in patients underwent gastrectomy. Oncotarget. 2017;8(14):23376–88.
40. Song GM, Tian X, Zhang L, Ou YX, Yi LJ, Shuai T, et al. Immunonutrition support for patients undergoing surgery for gastrointestinal malignancy: preoperative, postoperative, or perioperative? A Bayesian network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2015;94(29):e1225.
41. Klek S, Kulig J, Sierzega M, Szybinski P, Szczepanek K, Kubisz A, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. Ann Surg. 2008;248(2):212–20.
42. Marano L, Porfidia R, Pezzella M, Grassia M, Petrillo M, Esposito G, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol. 2013;20(12):3912–8.
43. Ward-Boahen D, Wallace-Kazer M. Improving surgical outcomes in pancreatic surgery with preoperative nutrition. J Adv Pract Oncol. 2014;5(2):100–6.
44. Hamza N, Darwish A, O'Reilly DA, Denton J, Sheen AJ, Chang D, et al. Perioperative enteral immunonutrition modulates systemic and mucosal immunity and the inflammatory response

in patients with periampullary cancer scheduled for pancreaticoduodenectomy: a randomized clinical trial. Pancreas. 2015;44(1):41–52.
45. Aida T, Furukawa K, Suzuki D, Shimizu H, Yoshidome H, Ohtsuka M, et al. Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy. Surgery. 2014;155(1):124–33.
46. Suzuki D, Furukawa K, Aida T, Uno H, Miyauchi Y, Shimizu H, et al. Effects of immunonutrition on postoperative complication, stress responses, and cell-mediated immunity after pancreaticoduodenectomy: results from two randomized controlled studies. Clin Nutr. 2014;33:S137–8. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/077/CN-01053077/frame.html.
47. Probst P, Ohmann S, Klaiber U, Huttner FJ, Billeter AT, Ulrich A, et al. Meta-analysis of immunonutrition in major abdominal surgery. Br J Surg. 2017;104(12):1594–608.
48. Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg. 2006;243(1):89–95.
49. Lyman GH. Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. Cancer. 2011;117(7):1334–49.
50. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(17):2189–204.
51. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg. 1997;84(6):750–9.
52. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev. 2008;4:CD005258.
53. Hayashi H, Morikawa T, Yoshida H, Motoi F, Okada T, Nakagawa K, et al. Safety of postoperative thromboprophylaxis after major hepatobiliary-pancreatic surgery in Japanese patients. Surg Today. 2014;44(9):1660–8.
54. Tzeng CW, Katz MH, Lee JE, Fleming JB, Pisters PW, Vauthey JN, et al. Predicting the risks of venous thromboembolism versus post-pancreatectomy haemorrhage: analysis of 13,771 NSQIP patients. HPB. 2014;16(4):373–83.
55. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43(3):263–309.
56. Bozzetti F, Mariani L. Perioperative nutritional support of patients undergoing pancreatic surgery in the age of ERAS. Nutrition. 2014;30(11-12):1267–71.
57. Buscemi S, Damiano G, Palumbo VD, Spinelli G, Ficarella S, Lo Monte G, et al. Enteral nutrition in pancreaticoduodenectomy: a literature review. Nutrients. 2015;7(5):3154–65.
58. Akizuki E, Kimura Y, Nobuoka T, Imamura M, Nagayama M, Sonoda T, et al. Reconsideration of postoperative oral intake tolerance after pancreaticoduodenectomy: prospective consecutive analysis of delayed gastric emptying according to the ISGPS definition and the amount of dietary intake. Ann Surg. 2009;249(6):986–94.
59. Lassen K, Revhaug A. Early oral nutrition after major upper gastrointestinal surgery: why not? Curr Opin Clin Nutr Metab Care. 2006;9(5):613–7.
60. Gerritsen A, Besselink MG, Gouma DJ, Steenhagen E, Borel Rinkes IH, Molenaar IQ. Systematic review of five feeding routes after pancreatoduodenectomy. Br J Surg. 2013;100(5):589–98; discussion 99.
61. Gerritsen A, Wennink RAW, Besselink MGH, Van Santvoort HC, Tseng DSJ, Steenhagen E, et al. Early oral feeding after pancreatoduodenectomy enhances recovery without increasing morbidity. HPB. 2014;16(7):656–64.

62. Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg. 2008;247(5):721–9.
63. Fujii T, Nakao A, Murotani K, Okamura Y, Ishigure K, Hatsuno T, et al. Influence of food intake on the healing process of postoperative pancreatic fistula after pancreatoduodenectomy: a multi-institutional randomized controlled trial. Ann Surg Oncol. 2015;22(12):3905–12.
64. Braga M, Capretti G, Pecorelli N, Balzano G, Doglioni C, Ariotti R, et al. A prognostic score to predict major complications after pancreaticoduodenectomy. Ann Surg. 2011;254(5):702–7; discussion 7–8.
65. Gerritsen A, Besselink MG, Cieslak KP, Vriens MR, Steenhagen E, van Hillegersberg R, et al. Efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreaticoduodenectomy. J Gastrointest Surg. 2012;16(6):1144–51.
66. Padussis JC, Zani S, Blazer DG, Tyler DS, Pappas TN, Scarborough JE. Feeding jejunostomy during Whipple is associated with increased morbidity. J Surg Res. 2014;187(2):361–6.
67. Waliye HE, Wright GP, McCarthy C, Johnson J, Scales A, Wolf A, et al. Utility of feeding jejunostomy tubes in pancreaticoduodenectomy. Am J Surg. 2017;213(3):530–3.
68. Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients. 2017;9(3):07.
69. Qinghua W, Qiangpu C. Jejunal tube feeding and pancreatoduodenectomy. Hepato-Gastroenterology. 2012;59(120):2653–6.
70. Seres DS, Valcarcel M, Guillaume A. Advantages of enteral nutrition over parenteral nutrition. Ther Adv Gastroenterol. 2013;6(2):157–67.
71. Zhao XF, Wu N, Zhao GQ, Liu JF, Dai YF. Enteral nutrition versus parenteral nutrition after major abdominal surgery in patients with gastrointestinal cancer: a systematic review and meta-analysis. J Investig Med. 2016;64(5):1061–74.
72. Lee SH, Lee JG. Early enteral nutrition still has advantages in patients undergoing pancreaticoduodenectomy. J Thorac Dis. 2016;8(10):E1340–E2.
73. Lu JW, Liu C, Du ZQ, Liu XM, Lv Y, Zhang XF. Early enteral nutrition vs parenteral nutrition following pancreaticoduodenectomy: experience from a single center. World J Gastroenterol. 2016;22(14):3821–8.
74. Perinel J, Mariette C, Dousset B, Sielezneff I, Gainant A, Mabrut J, et al. Early enteral versus total parenteral nutrition in patients undergoing pancreaticoduodenectomy: a randomized multicenter controlled trial (NUTRI DPC). U Eur Gastroenterol J Conf. 2016;4(5 Suppl 1):A92–3. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/904/CN-01438904/frame.html.
75. Probst P, Keller D, Steimer J, Gmur E, Haller A, Imoberdorf R, et al. Early combined parenteral and enteral nutrition for pancreaticoduodenectomy - retrospective cohort analysis. Ann Med Surg. 2016;6:68–73.
76. Zhu X, Wu Y, Qiu Y, Jiang C, Ding Y. Comparative analysis of the efficacy and complications of nasojejunal and jejunostomy on patients undergoing pancreaticoduodenectomy. J Parenter Enter Nutr. 2014;38(8):996–1002.
77. Okabayashi T, Kobayashi M, Nishimori I, Sugimoto T, Akimori T, Namikawa T, et al. Benefits of early postoperative jejunal feeding in patients undergoing duodenohemipancreatectomy. World J Gastroenterol. 2006;12(1):89–93.
78. Takagi K, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, et al. Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. Clin Nutr. 2019;38:174. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/089/CN-01450089/frame.html.
79. Poves I, Burdio F, Morato O, Iglesias M, Radosevic A, Ilzarbe L, et al. Comparison of perioperative outcomes between laparoscopic and open approach for pancreatoduodenectomy: the PADULAP randomized controlled trial. Ann Surg. 2018;268(5):731–9.

80. Palanivelu C, Senthilnathan P, Sabnis SC, Babu NS, Srivatsan Gurumurthy S, Anand Vijai N, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. Br J Surg. 2017;104(11):1443–50.
81. de Rooij T, van Hilst J, Bosscha K, Dijkgraaf MG, Gerhards MF, Groot Koerkamp B, et al. Minimally invasive versus open pancreatoduodenectomy (LEOPARD-2): study protocol for a randomized controlled trial. Trials. 2018;19(1):1.
82. van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol Hepatol. 2019;4(3):199–207.
83. Zhao W, Liu C, Li S, Geng D, Feng Y, Sun M. Safety and efficacy for robot-assisted versus open pancreaticoduodenectomy and distal pancreatectomy: a systematic review and meta-analysis. Surg Oncol. 2018;27(3):468–78.

Chapter 39
The Elderly Patient with Pancreatic Cancer: Trends and Medical Oncology

Lydia van der Geest, Johanneke Portielje, and Hanneke Wilmink

Take Home Messages

- A double aging is taking place in Europe and the incidence of pancreatic cancer is highest in the elderly.
- Although very few elderly patients receive chemotherapy, older age and a less favourable performance status are prognostic for poor outcomes in randomised and non-randomised studies.
- In elderly patients, physical fitness is overestimated by performance status alone in comparison with a Comprehensive Geriatric Assessment (CGA).
- Studies investigating CGA and chemotherapy-treatment in elderly patients with pancreatic cancer are scarce.

Pearls and Pitfalls

- Pearl: Comprehensive Geriatric Assessment (CGA) may have added value in clinical practice of prehabilitation and rehabilitation of elderly patients.
- Pitfall: Due to 'rejuvenation' of elderly patients, an age cut-off for planned subgroup analysis in randomised studies should be carefully defined (in the past usually at 65 years, but should be higher).

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Future Perspectives

- Benefits and risks of contemporary first-line and second-line chemotherapy regimens in elderly patients need to be investigated in more detail, taking into account performance status, organ function and other geriatric aspects from Comprehensive Geriatric Assessment (CGA).

39.1 Introduction

Pancreatic cancer typically is a cancer of the elderly. The incidence of pancreatic cancer increases sharply with advanced age from ≤1 per 100,000 person years in the age group 15–44 years until more than 70 per 100,000 in the age group over 75 years [1].

39.2 An Aging European Population

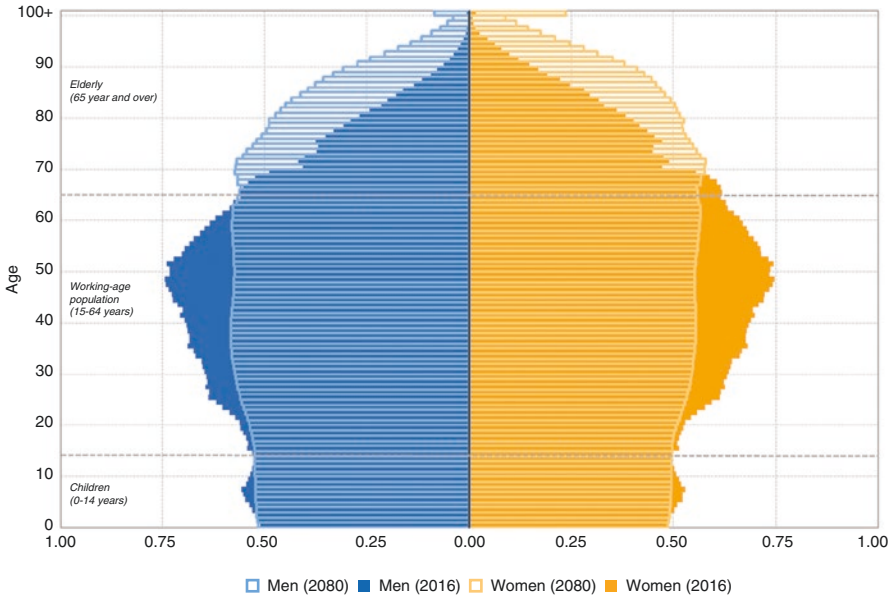
In many Western countries, a so-called 'double aging' is taking place; the 'baby boom' generation born after the second World War is reaching an older age and people are getting older due to improved health care and living conditions. In the next three decades, the proportion and absolute number of older persons in these populations will continue to rise.

Until 2070, the proportion of persons aged 65 and over will rise from 19% to 29% of the population and the group aged 80 and over will increase from 5% to 13%, becoming almost as large as the young population under 15 years in 2070 (from 16% to 15%). By 2070, Japan, the EU and China will have the oldest populations among large economies worldwide [2] (Fig. 39.1).

39.3 Definition of 'the Elderly'

No clear definition of 'the elderly' can be given. In Western countries, persons were usually defined as 'elderly' when they reach a chronological age of 65 years [3], which in many countries is the starting age at which pension benefits can be received. However, there is no clear medical or biological evidence to support this definition and remarkably, in the past decades, a process of 'rejuvenation' seems to have taken place [4].

Between elderly persons of the same age, a large variation in physical functioning exists. The process of aging is characterised by a gradual loss of functional reserve of several organ systems, increased prevalence of chronic diseases and enhanced susceptibility to stressors like cancer and cancer treatment [5]. Physiologic changes that are related to aging affect drug metabolism, such as the altered gastric, hepatic and renal function, or the altered proportion and distribution of body fat and



Note: 2016, estimates. 2080: projections.
Source: Eurostat (online data codes: demo_pjan and proj_15npms)

Fig. 39.1 European population demographic, projection 2016–2080

water in elderly patients [6]. A different pace of this process in individuals results in a large heterogeneity within the elderly age group.

Elderly patients are underrepresented in the available evidence on which evidence-based guidelines are based [7, 8]. Inclusion and exclusion criteria of most clinical trials investigating systemic treatments explicitly exclude patients with poor performance status or multimorbidity. In addition, many clinical trials use an upper age limit, usually at 75 years of age.

Older people may have multiple, complex and overlapping health problems. However, when chronological age is used as a summary or surrogate measurement to physical functioning, decision-making will result in both under-treatment and over-treatment in various practice settings. Furthermore, tools that intend to individualise treatment to patient characteristics often contain 'chronological age' instead of age-associated domains of functioning ('functional age'), for example the prognostic model 'Predict' for early-stage breast cancer (https://breast.predict.nhs.uk).

39.4 Pancreatic Cancer

The number of patients with newly diagnosed pancreatic cancer in Europe has increased from circa 96,000 in 2008 to 132,600 in 2018 (+38%) [9, 10], and will further increase with the aging European population. More than half of this patient

population is aged 70 years or older at time of diagnosis and about 20–29% of patients is 80 years or older [11, 12].

The vast majority of patients with pancreatic cancer present with advanced disease, either locally advanced (irresectable) or metastatic disease (>50% or patients). Many patients suffer from symptoms such as weight loss, sarcopenia and fatigue. Elderly patients are at increased risk to die soon after diagnosis of pancreatic cancer [13, 14]. For example, in a population-based study from the Netherlands nearly half of octogenarians with metastatic pancreatic cancer died within 30 days after diagnosis compared with one-fifth of patients under 70 years of age (43% and 19%, respectively) [14].

With rising age of patients with pancreatic cancer, chemotherapy use is far less likely. This age pattern was found in patients with advanced disease (metastatic or locally advanced) [14–19], as well as in the adjuvant treatment setting [20–23]. Especially in the oldest age groups a strong selection took place and only few patients over 80 years of age received chemotherapy [14, 19].

Given the high symptom burden and the short life expectancy, clinical trials in pancreatic cancer focus on patients with a higher likelihood of obtaining a clinical benefit [24]. This patient group usually has a relatively good performance status (ECOG/WHO PS 0–1 or Karnofsky PS 80–100%), which is a minority of patients in everyday clinical practice. In addition, survival outcomes of chemotherapy-treated patients in daily clinical practice often are less favourable compared with the original trial population, since chemotherapy is often provided to patients who were not eligible for the clinical trial [25]. In randomised clinical trials and in case series, survival outcomes after gemcitabine were between 5 and 9 months in elderly patients [18, 26, 27]. Nowadays more potent but also more toxic chemotherapy regimens are available, with limited experience in the older population.

39.5 Metastatic Pancreatic Cancer

A significant breakthrough for patients with metastatic pancreatic cancer was achieved with the FOLFIRINOX regimen (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) in the pivotal PRODIGE-4/ACCORD-11 trial (median OS 11.1, versus 6.8 months in gemcitabine alone) [28]. In addition, the MPACT trial showed a survival benefit of the combination gemcitabine with nab-paclitaxel over gemcitabine alone (median OS 8.5 and 6.7 months, respectively) [28, 29]. Since the PRODIGE-4 trial excluded patients over 75 years of age or performance status higher than one [28], enrolled patients were relatively young (median 61 years, range 28–76) and fit (PS > 1: 0.3%) compared with patients in the MPACT trial (median age 63 years, range 27–88 years, ≥75 years: 10%, PS > 1: 8%) [29]. Age and performance status of patients in the MPACT trial seemed more in line with chemotherapy-treated patients in clinical practice (median age: 63–70 years, ≥75 years: 8–34%, PS > 1: 11%) [14, 30, 31]. In the PRODIGE and the MPACT trials, either age over 65 years (PRODIGE), or a less favourable performance status (MPACT), were identified as prognostic factors for an impaired survival.

Also in non-randomised studies, patients receiving FOLFIRINOX were substantially younger (median age 60–63 years) compared with patients treated with nab-paclitaxel plus gemcitabine (median 68–71 years) or gemcitabine therapy (median 69–78 years) [30–32]. A similar pattern was found for performance status; 4%, 10% and 20% of patients with FOLFIRINOX, nab-paclitaxel with gemcitabine and gemcitabine, respectively, had a PS > 1 [31].

39.5.1 Elderly Patients and Gemcitabine-Based Chemotherapy

In several case series, mostly from single institutions, it was suggested that no clear survival differences between younger and older chemotherapy-treated patients exist [18, 27, 33]. However, median overall survival was quite high (mOS 8–9 months) and some of these studies enrolled patients with locally advanced pancreatic cancer as well. In population-based studies performed in the gemcitabine era [14, 30], overall survival of chemotherapy-treated patients was worse (median OS 5.0–5.7 months) compared with the gemcitabine arms in the MPACT and PRODIGE studies. Especially chemotherapy-treated elderly patients over 75 years of age experienced a worse overall survival (<70, 70–74, 75–79, ≥80 years: median OS 25, 26, 19 and 16 weeks, p = 0.003, HR[75–79, ≥80 vs. <70 years] > 1) [14]. Possibly poor performance status, complications or early discontinuation may have added to observed survival disparities.

39.5.2 Elderly Patients and Contemporary Chemotherapy Regimens

The survival benefit from FOLFIRINOX and gemcitabine plus nab-paclitaxel over gemcitabine monotherapy went along with an increased risk of grade 3+ toxicities that restricts the applicability of both regimens. To decrease the incidence and severity of adverse events while maintaining efficacy results, drug dose and schedule modifications were investigated [34–37].

Some studies explored outcomes of contemporary chemotherapy regimens in elderly patients (defined as either 65 or 75 years or older) and found small non-significant or no overall survival differences according to age [30, 35, 36]. In a large population-based study in Canada investigating patients with metastatic pancreatic cancer, the FOLFIRINOX-group (n = 784, median age 63 years, 4% >75 years) showed no survival disparities according to age, but overall survival seemed less favourable than in the original PRODIGE trial (median OS 8.2 versus 11.1 months, respectively) [28, 30]. Other studies included patients with both metastatic and locally advanced pancreatic cancer and thus survival could not be compared with the corresponding randomised studies [35, 36].

Studies investigating contemporary chemotherapy treatment specifically in patients with a less favourable performance status are scarce. In the FRAGRANCE-trial, only

patients with PS 2 and unresectable pancreatic cancer were enrolled (locally advanced and metastatic disease); patients were randomised between modified schemes of nab-paclitaxel with gemcitabine [34]. Median progression-free survival (5.7–6.7 months) and 6-months overall survival (63–69%) in this study were encouraging, but again less favourable compared to the original trials in metastatic disease only.

39.6 Adjuvant Treatment for (Borderline) Resectable Pancreatic Cancer

No upper age limit was used for inclusion of patients in randomised studies on adjuvant treatment following resection for pancreatic cancer [38–41]. All these randomised studies enrolled some octogenarians (oldest age 81–85 years) and median age of patients (61–65 years) was very similar to patients treated with adjuvant chemotherapy in an international study with population-based data from the USA, Belgium, The Netherlands, Slovenia and Norway (median age 61–65 years) [42]. Furthermore, in all randomised studies investigating 5-fluorouracil/leucovorin or gemcitabine-based regimens, a less favourable PS was permitted (3–12% PS 2), [38–40] which was similar to a nationwide cohort (6%) [42]. Only in the most recent PRODIGE-24 study (FOLFIRINOX versus gemcitabine) a PS 0–1 was required [41].

A less favourable performance status only seemed a prognostic factor for survival in the ESPAC-3 study that included the highest proportion of patients with PS 2 (12%) [39]. In other randomized studies investigating 5-fluorouracil/leucovorin or gemcitabine-based regimens, an older age and a less favourable performance status did not seem a prognostic factor [21, 22, 38, 40, 42]. However, in the PRODIGE-24 study no significant benefit was found for FOLFIRINOX over gemcitabine in patients aged 70 years or older [41].

39.7 Second Line Treatment

Despite the aggressive behaviour of pancreatic cancer, up to half of patients seem still eligible for a second-line treatment [31, 32, 43], especially following FOLFIRINOX [32]. Patients need to be in a good physical condition, with adequate haematological, hepatic and renal function. Thus far, no randomised studies are available following FOLFIRINOX. In patients with metastatic disease previously treated with gemcitabine-based therapy, the NAPOLI-1 trial showed a prolonged overall survival for nanoliposomal irinotecan with fluorouracil/leucovorin compared with fluorouracil/leucovorin monotherapy (mOS 6.2 vs. 4.2 months, respectively) [44]. Age and performance status of enrolled patients in the NAPOLI-1 study were largely comparable with the MPACT study on first-line treatment for metastatic disease, with median age 62–63 years (25% ≥70 years) and 8.5% of patients with PS > 1. Among other factors, performance status, not age, was prognostic for overall survival.

39.8 Guidelines for Chemotherapy Treatment in Elderly Patients

As of 2012, Clinical Practice Guidelines for pancreatic adenocarcinoma from the European Society for Medical and Digestive Oncology (ESMO-ESDO), as well as the American Society of Clinical Oncology Clinical Practice Guideline (ASCO) and the American National Comprehensive Cancer Network (NCCN), distinguished between a good and poor performance status of patients with regard of recommendations on the type of adjuvant and palliative chemotherapy (Appendix) [45–50]. These guidelines did not specify age per se as a decision criterium to choose a type of chemotherapy in advanced pancreatic cancer. For adjuvant chemotherapy, the ESMO-group added a recommendation on age based on impaired Disease-Free Survival results in patients over 70 years in the PRODIGE-24 trial [41]. Although performance status was considered more important for treatment-decisions than age, it is still a rather crude measure for the heterogeneity in 'functional age' of elderly patients.

39.9 Comprehensive Geriatric Assessment

Performance status alone overestimates the physical fitness for chemotherapy treatment of elderly patients in comparison with a Comprehensive Geriatric Assessment (CGA) [51]. As recommended by the Society of Geriatric Oncology (SIOG) in 2014, the following domains should be evaluated: comorbidity and functional status, cognition and mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes (e.g. dementia, delirium, falls, incontinence, osteoporosis) [52]. This assessment can be complemented with biological markers that are associated with the process of aging [53], such as the inflammatory index. Factors that may delay or preclude the maximal recovery potential from illnesses should also be addressed [54].

In several types of cancer, a CGA has been shown to predict treatment outcomes and has been used to tailor treatment to the results of the assessment [55–58]. CGA predicts functional decline, chemotherapy toxicity, morbidity, and mortality [54]. Geriatric Assessment frequently reveals deficits in elderly patients that are not routinely captured in a standard examination, [51] potentially improving selection of elderly patients for cancer treatments or oncology treatment outcomes like completion rates, treatment modifications and grade 3–4 toxicities [52, 59]. Dose adjustment in accordance with the functioning of specific organ systems and review of possible drug-drug interactions are crucial for the tolerance of chemotherapy regimens and oncologic outcomes in elderly patients [6, 53]. Thus far, the systematic use of a Comprehensive Geriatric Assessment specifically for tailoring of chemotherapy treatment in patients with advanced pancreatic cancer seems scarce. For example, the GrandPax study uses a CGA-driven stratification of elderly patients

(≥70 years) with metastatic pancreatic cancer for nab-paclitaxel and gemcitabine versus gemcitabine alone versus best supportive care, with re-assignment when their CGA performance declines [37]. It was hypothesised that with personalised GA-directed treatment, more patients may benefit from the combination treatment. No data are yet available.

Recently, the American Society of Clinical Oncology (ASCO) Guidelines for Geriatric Oncology were published for assessment and management of vulnerable older patients (≥65 years) receiving chemotherapy (Table 39.1) [60]. For example, if chemotherapy is considered, the Cancer and Aging Research Group (CARG) or Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) tools can be used to identify patients at increased risk of toxicity from chemotherapy [57, 58, 61].

Table 39.1 Geriatric Assessment (GA) domains and possible interventions in case of impairment, recommended for all patients aged 65 years and older

GA domains	Recommended tool and score signifying impairment	Consider other options	GA guided interventions in case of impairment
Function and falls	IADLs (≤5 min): dependence on any task signifies impairment. Single item: "How many falls have you had over the last 6 months (or since the last visit)?" One or more recent falls.	Any ADL deficit is used for characterization of frailty. Consider objective measure of physical performance such as SPPB, TUG, or gait speed.	Physical therapy and/or occupational therapy referrals to prescribe strength and balance training, assist device evaluation, home exercise program, and safety evaluation. Fall prevention discussion. Home safety evaluation.
Comorbidity and polypharmacy	Robust review of chronic medical conditions and medications through routine history (routine care): three or more chronic health problems or one or more serious health problems.	Consider validated tools such as CIRS-G or Charlson. History, CIRS-G, and OARS comorbidity recommended by experts.	Involve caregiver in discussions to assess risks of therapy and management of comorbidities. Involve primary care physician and/or geriatrician in decision making for treatment and management of comorbidities; consider referral to geriatrician. Review medication list and minimize medications as much as possible; consider involving a pharmacist. Assess adherence to medications; have patient bring in medications to review.

Table 39.1 (continued)

GA domains	Recommended tool and score signifying impairment	Consider other options	GA guided interventions in case of impairment
Cognition	Mini-Cog (≤5 min): an abnormal test is defined by zero words recalled OR one to two words recalled + abnormal clockdrawing test. OR BOMC test (≤5 min): a score of 6 or greater identifies patients who have moderate deficits, and a cut point of 11 or greater identifies patients with severe cognitive impairment.	Multiple tools are available for cognitive assessment. The MMSE has more robust data for prediction of outcomes in older patients with cancer and has been shown to predict chemotherapy toxicity; it is included in the CRASH tool [58]. The MOCA is also used by geriatricians. Both MMSE and MOCA are considerably longer than Mini-Cog and BOMC.	Assess decision-making capacity and ability to consent for treatment. Identification of health care proxy and involve proxy in decision making for treatment, including signing consent forms with patient. Delirium risk counseling for patient and family. Medication review to minimize medications with higher risk of delirium. Consider further work-up with geriatrician or cognitive specialist.
Depression	GDS 15 items (≤5 min): a score of >5 suggests depression and requires follow-up.	GDS recommended also by ASCO guidelines for depression. The PHQ-9 is an alternative and is also recommended by ASCO guidelines for depression.	Consider referral for psychotherapy/ psychiatry. Consider cognitive-behavioral therapy. Social work involvement. Consider pharmacologic therapy.
Nutrition	Unintentional weight loss (>10% weight loss from baseline weight); BMI <21 kg/m^2.	Consider G8 and MNA as alternatives; both are associated with mortality in older patients with cancer.	Nutrition counselling. Referral to nutritionist/ dietician. Assess need for extra support for meal preparation and institute support interventions if necessary (e.g., caregiver, Meals-on-Wheels).
Combination of GA domains: risk of chemotherapy toxicity	CARG toxicity tool: provides estimates for overall risk of grade 3 to 5 chemotherapy toxicity (5 min)[a]. OR CRASH tool: provides estimates separately for risk of grade 3 hematologic and grade 3 to 4 non-hematologic toxicity (20–30 min)[b].		

(continued)

Table 39.1 (continued)

GA domains	Recommended tool and score signifying impairment	Consider other options	GA guided interventions in case of impairment
Combination of GA domains: screening	Tools that can be used as a screening tool to identify older patients who need more comprehensive GA. G8 (5–10 min)[c]: Score of ≥14 signifies impairment. Derived from the MNA. VES-13 (5–10 min)[d]: Score of ≥3 is associated with mortality and chemotherapy toxicity in older patients with cancer. A score of ≥7 has been shown to be associated with functional decline.	In addition: Investigate social support, i.e. living condition, marital status. Estimate (non-cancer) life expectancy using Schonberg Index or Lee Index, presented on ePrognosis (https://eprognosis.ucsf.edu).	Perform full Comprehensive Geriatric Assessment and/or consider referral to geriatrician.

Tables 1 and 2 combined from Mohile et al. American Society of Clinical Oncology (ASCO) guideline for Geriatric Oncology. J Clin Oncol 2018 [60]. See also Table 1 in: Wildiers et al. International Society of Geriatric Oncology (SIOG) recommendations on Geriatric Assessment. J Clin Oncol 2014 [52]

Abbreviations (alphabetical): *ADL* activity of daily living, *BMI* body mass index, *BOMC* Blessed Orientation-Memory-Concentration, *CARG* Cancer and Aging Research Group, *CIRS-G* Cumulative Illness Rating Score-Geriatrics, *CRASH* Chemotherapy Risk Assessment Scale for High-Age Patients, *ECOG PS* Eastern Cooperative Oncology Group performance status, *G8* Geriatric-8, *GA* Geriatric Assessment, *GDS* Geriatric Depression Scale, *IADL* Instrumental Activity of Daily Living, *LDH* lactate dehydrogenase, *Mini-Cog* screening tool for cognitive impairment, *MMSE* Mini-Mental State Examination, *MNA* Mini Nutritional Assessment, *MOCA* Montreal Cognitive Assessment, *OARS* Older Americans Resources and Services, *PHQ-9* Patient Health Questionnaire-9, *PRO* Patient-Reported Outcome, *SPPB* Short Physical Performance Battery, *TUG* Timed Up and Go, *VES-13* Vulnerable Elders Survey-13

[a]Eleven items: prior falls (one or more vs. none), hearing problems (deaf to excellent), limitations in walking one block (limited a lot, limited a little, not limited), difficulties with taking medications, interference of social activities by physical health and/or emotional problems (all of the time to none of the time) as well as age, height, weight, gender, cancer type (GI vs. genitourinary vs. other), dosage (standard vs. dose reduced), number of chemotherapy agents (mono vs. poly), haemoglobin level, and creatinine clearance

[b]Assessment of risk of hematologic toxicity includes diastolic blood pressure (>72 mmHg), IADL score (<26), and LDH (>459 U/L). Assessment of risk of non-hematologic toxicity includes ECOG PS, MMSE (<30), and MNA (<28). Chemotherapy intensity is assessed with MAX2 index = (most frequent grade 4 hematologic toxicity + most frequent grade 3–4 non/hematologic toxicity) divided by 2

[c]Eight items covering appetite, weight loss, neuropsychological problems, BMI, number of medications, patient selfrated health, and age

[d]Thirteen items including age, self-rated health, common functional tasks, and ability to complete physical activities

39.10 Decision-Making: The Elderly Patients' Perspective

Treatment goals, regimen-specific toxicities, and quality of life and survival benefit need to be discussed with elderly patients. Elderly patients weight cancer treatment options and treatment goals differently from younger patients. With rising age, quality of life and maintaining functional independence become more important than overall survival [62, 63], but preferences may vary widely, depending on physical, psychological and social situation. The potential benefits of cancer treatment in terms of survival and quality of life must be discussed and well balanced against (time spent with) symptoms or treatment complications. It has been shown that well-informed healthy elderly patients may actively choose to withhold from pancreatic cancer treatment [64].

Shared decision-making (SDM) is increasingly valued by patients and clinicians, but may be especially difficult in elderly patients with pancreatic cancer because of the tremendous lack of evidence about outcomes of treatment at increased age. In addition, elderly patients are less likely to take an active role in SDM [65].

39.11 Conclusion

Elderly patients receiving chemotherapy are strongly selected. Age distribution of patients enrolled in randomised studies seemed largely representative for everyday clinical practice, with the exception of studies that investigated FOFIRINOX. Older age and or less favourable performance status were prognostic for poor outcomes in many randomised studies, though a higher age cut-off at 70 or 75 years should be used for planned subgroup analyses in elderly patients. Further prospective and retrospective studies are necessary to provide insight in benefits and risks of contemporary first-line and second-line chemotherapy regimens in elderly patients, taking into account performance status, organ function and other geriatric aspects from Comprehensive Geriatric Assessment (CGA).

39.12 Appendix: Recommendations in International Clinical Practice Guidelines on Chemotherapy According to Age and Performance Status

	Adjuvant chemotherapy for resected pancreatic cancer	Chemotherapy for metastatic pancreatic cancer[a]	Second line treatment in metastatic pancreatic cancer
ESMO	• PS 0–1 mFOLFIRINOX • PS 2, age >70 or contraindication to FOLFIRINOX: gemcitabine + capecitabine • PS >2: gemcitabine monotherapy [48]	• PS 0–1 and bilirubin <1.5 ULN: combination therapy FOLFIRINOX or gemcitabine + nab-paclitaxel • PS 2 due to heavy tumour load: gemcitabine + nab-paclitaxel • PS 2 or bilirubin >1.5 × ULN: gemcitabine monotherapy • PS 3–4 or severe comorbidities: no chemotherapy (symptomatic treatment) [46]	• For fit patients: nanoliposomal irinotecan + fluorouracil (following progression on gemcitabine-based chemotherapy) [48]
ASCO	• mFOLFIRINOX • In case of concerns for toxicity or tolerance: gemcitabine + capecitabine or monotherapy gemcitabine or fluorouracil can be offered [49]	• PS 0–1 and favourable comorbidity: FOLFIRINOX or gemcitabine + nab-paclitaxel • PS 2 or comorbidity profile that precludes more aggressive regimens: gemcitabine or fluorouracil monotherapy [47]	• PS 0–1 and favourable comorbidity: nanoliposomal irinotecan + fluorouracil (following gemcitabine + nab-paclitaxel) or nab-paclitaxel + gemcitabine can be offered (following FOLFIRINOX) • If nanoliposomal irinotecan not available: fluorouracil + irinotecan or fluorouracil + oxaliplatin may be considered • PS 2 or comorbidity concerns: can be considered gemcitabine or fluorouracil [47]

	Adjuvant chemotherapy for resected pancreatic cancer	Chemotherapy for metastatic pancreatic cancer[a]	Second line treatment in metastatic pancreatic cancer
NCCN	• Good PS (0–1): mFOLFIRINOX • Otherwise: gemcitabine + capecitabine or gemcitabine monotherapy or fluorouracil monotherapy [50]	• Good PS: FOLFIRINOX or gemcitabine combination therapy [good PS defined as PS 0–1] • Poor PS: gemcitabine monotherapy or gemcitabine + nab-paclitaxel (if Karnofsky PS ≥ 70%) or palliative treatment [poor PS defined as WHO PS > 1 or poor nutritional status or not patent biliary stent or poor pain control] [45]	• Good PS: nanoliposomal irinotecan + fluorouracil (following gemcitabine + nab-paclitaxel) or gemcitabine-based (following FOLFIRINOX) [45]

[a]Recommendations for locally advanced pancreatic cancer are largely extrapolated from evidence in metastatic disease (ASCO, NCCN) or recommendations are not updated due to a lack of clear evidence in this patient group (ESMO)

References

1. Minicozzi P, Cassetti T, Vener C, Sant M. Analysis of incidence, mortality and survival for pancreatic and biliary tract cancers across Europe, with assessment of influence of revised European age standardisation on estimates. Cancer Epidemiol. 2018;55:52–60.
2. The 2018 Ageing Report: Economic and Budgetary Projections for the EU Member States (2016–2070). European Economy Institutional Paper 079. Luxembourg: European Commission Economic and Financial Affairs 25 May 2018.
3. WHO Health statistics and information systems: World Health Organization. 2019. https://www.who.int/healthinfo/survey/ageingdefnolder/en/.
4. Ouchi Y, Rakugi H, Arai H, Akishita M, Ito H, Toba K, et al. Redefining the elderly as aged 75 years and older: proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. Geriatr Gerontol Int. 2017;17(7):1045–7.
5. Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. Surg Oncol. 2010;19(3):117–23.
6. Garcia G, Odaimi M. Systemic combination chemotherapy in elderly pancreatic cancer: a review. J Gastrointest Cancer. 2017;48(2):121–8.
7. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341(27):2061–7.
8. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharm Pract (Granada). 2014;12(4):489.

9. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46(4):765–81.
10. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356–87.
11. Coupland VH, Kocher HM, Berry DP, Allum W, Linklater KM, Konfortion J, et al. Incidence and survival for hepatic, pancreatic and biliary cancers in England between 1998 and 2007. Cancer Epidemiol. 2012;36(4):e207–14.
12. van der Geest LG, Besselink MG, van Gestel YR, Busch OR, de Hingh IH, de Jong KP, et al. Pancreatic cancer surgery in elderly patients: balancing between short-term harm and long-term benefit. A population-based study in the Netherlands. Acta Oncol. 2016;55(3):278–85.
13. Fest J, Ruiter R, van Rooij FJ, van der Geest LG, Lemmens VE, Ikram MA, et al. Underestimation of pancreatic cancer in the National Cancer Registry - reconsidering the incidence and survival rates. Eur J Cancer. 2016;72:186–91.
14. van der Geest LGM, Haj Mohammad N, Besselink MGH, Lemmens V, Portielje JEA, van Laarhoven HWM, et al. Nationwide trends in chemotherapy use and survival of elderly patients with metastatic pancreatic cancer. Cancer Med. 2017;6(12):2840–9.
15. van der Geest LGM, van Eijck CHJ, Groot Koerkamp B, Lemmens V, Busch OR, Vissers PAJ, et al. Trends in treatment and survival of patients with nonresected, nonmetastatic pancreatic cancer: a population-based study. Cancer Med. 2018;7(10):4943–51.
16. Oberstein PE, Hershman DL, Khanna LG, Chabot JA, Insel BJ, Neugut AI. Uptake and patterns of use of gemcitabine for metastatic pancreatic cancer: a population-based study. Cancer Investig. 2013;31(5):316–22.
17. Enewold L, Harlan LC, Tucker T, McKenzie S. Pancreatic cancer in the USA: persistence of undertreatment and poor outcome. J Gastrointest Cancer. 2015;46(1):9–20.
18. Li D, Capanu M, Yu KH, Lowery MA, Kelsen DP, O'Reilly EM. Treatment, outcomes, and clinical trial participation in elderly patients with metastatic pancreas adenocarcinoma. Clin Colorectal Cancer. 2015;14(4):269–76.e1.
19. Khanal N, Upadhyay S, Dahal S, Bhatt VR, Silberstein PT. Systemic therapy in stage IV pancreatic cancer: a population-based analysis using the National Cancer Data Base. Ther Adv Med Oncol. 2015;7(4):198–205.
20. Wu W, He J, Cameron JL, Makary M, Soares K, Ahuja N, et al. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol. 2014;21(9):2873–81.
21. Nagrial AM, Chang DK, Nguyen NQ, Johns AL, Chantrill LA, Humphris JL, et al. Adjuvant chemotherapy in elderly patients with pancreatic cancer. Br J Cancer. 2014;110(2):313–9.
22. Bakens MJ, van der Geest LG, van Putten M, van Laarhoven HW, Creemers GJ, Besselink MG, et al. The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis. Cancer Med. 2016;5(10):2825–31.
23. Huang L, Jansen L, Balavarca Y, van der Geest L, Lemmens V, Van Eycken L, et al. Nonsurgical therapies for resected and unresected pancreatic cancer in Europe and USA in 2003–2014: a large international population-based study. Int J Cancer. 2018;143(12):3227–39.
24. Macarulla T, Carrato A, Diaz R, Garcia A, Laquente B, Sastre J, et al. Management and supportive treatment of frail patients with metastatic pancreatic cancer. J Geriatr Oncol. 2019;10(3):398–404.
25. Ueda A, Hosokawa A, Ogawa K, Yoshita H, Ando T, Kajiura S, et al. Treatment outcome of advanced pancreatic cancer patients who are ineligible for a clinical trial. Onco Targets Ther. 2013;6:491–6.
26. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.

27. Kuroda T, Kumagi T, Yokota T, Azemoto N, Hasebe A, Seike H, et al. Efficacy of chemotherapy in elderly patients with unresectable pancreatic cancer: a multicenter review of 895 patients. BMC Gastroenterol. 2017;17(1):66.
28. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
29. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
30. Karim S, Zhang-Salomans J, Biagi JJ, Asmis T, Booth CM. Uptake and effectiveness of FOLFIRINOX for advanced pancreatic cancer: a population-based study. Clin Oncol. 2018;30(1):e16–21.
31. Hegewisch-Becker S, Aldaoud A, Wolf T, Krammer-Steiner B, Linde H, Scheiner-Sparna R, et al. Results from the prospective German TPK clinical cohort study: treatment algorithms and survival of 1,174 patients with locally advanced, inoperable, or metastatic pancreatic ductal adenocarcinoma. Int J Cancer. 2019;144(5):981–90.
32. Abrams TA, Meyer G, Meyerhardt JA, Wolpin BM, Schrag D, Fuchs CS. Patterns of chemotherapy use in a U.S.-based cohort of patients with metastatic pancreatic cancer. Oncologist. 2017;22(8):925–33.
33. Hentic O, Dreyer C, Rebours V, Zappa M, Levy P, Raymond E, et al. Gemcitabine in elderly patients with advanced pancreatic cancer. World J Gastroenterol. 2011;17(30):3497–502.
34. Macarulla T, Pazo-Cid R, Guillen-Ponce C, Lopez R, Vera R, Reboredo M, et al. Phase I/II trial to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with pancreatic cancer and an ECOG performance status of 2. J Clin Oncol. 2019;37(3):230–8.
35. Ishimoto U, Kinoshita A, Hirose Y, Shibata K, Ishii A, Shoji R, et al. The efficacy and safety of nab paclitaxel plus gemcitabine in elderly patients over 75 years with unresectable pancreatic cancer compared with younger patients. Cancer Chemother Pharmacol. 2019;84(3):647–54.
36. Berger AK, Haag GM, Ehmann M, Byl A, Jager D, Springfeld C. Palliative chemotherapy for pancreatic adenocarcinoma: a retrospective cohort analysis of efficacy and toxicity of the FOLFIRINOX regimen focusing on the older patient. BMC Gastroenterol. 2017;17(1):143.
37. Betge J, Chi-Kern J, Schulte N, Belle S, Gutting T, Burgermeister E, et al. A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/− nab-paclitaxel in elderly pancreatic cancer patients (GrantPax). BMC Cancer. 2018;18(1):747.
38. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
39. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
40. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
41. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
42. Huang L, Balavarca Y, van der Geest L, Lemmens V, Van Eycken L, De Schutter H, et al. Development and validation of a prognostic model to predict the prognosis of patients who underwent chemotherapy and resection of pancreatic adenocarcinoma: a large international population-based cohort study. BMC Med. 2019;17(1):66.
43. Aprile G, Negri FV, Giuliani F, De Carlo E, Melisi D, Simionato F, et al. Second-line chemotherapy for advanced pancreatic cancer: which is the best option? Crit Rev Oncol Hematol. 2017;115:1–12.

44. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545–57.
45. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2017;15(8):1028–61.
46. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
47. Sohal DPS, Kennedy EB, Khorana A, Copur MS, Crane CH, Garrido-Laguna I, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36(24):2545–56.
48. Cancer of the Pancreas: ESMO clinical practice guidelines. eUpdate 15 March 2019: New treatment recommendations for pancreatic cancer 2019. https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas.
49. Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(20):2324–8.
50. Tempero MA, Malafa MP, Chiorean EG, Czito B, Scaife C, Narang AK, et al. Pancreatic adenocarcinoma, Version 1.2019. J Natl Compr Cancer Netw. 2019;17(3):202–10.
51. Wedding U, Kodding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol. 2007;64(1):1–9.
52. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32(24):2595–603.
53. Balducci L, Dolan D. Palliative care of cancer in the older patient. Curr Oncol Rep. 2016;18(12):70.
54. Ellis G, Gardner M, Tsiachristas A, Langhorne P, Burke O, Harwood RH, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2017;9:CD006211.
55. Paillaud E, Soubeyran P, Caillet P, Cudennec T, Brain E, Terret C, et al. Multidisciplinary development of the geriatric core dataset for clinical research in older patients with cancer: a French initiative with international survey. Eur J Cancer. 2018;103:61–8.
56. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, Schaar C, van Munster BC. The effect of a geriatric evaluation on treatment decisions for older cancer patients--a systematic review. Acta Oncol. 2014;53(3):289–96.
57. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29(25):3457–65.
58. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118(13):3377–86.
59. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, et al. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015;112(9):1435–44.
60. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;2018:JCO2018788687.
61. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. J Clin Oncol. 2016;34(20):2366–71.

62. Moth EB, Kiely BE, Martin A, Naganathan V, Della-Fiorentina S, Honeyball F, et al. Older adults' preferred and perceived roles in decision-making about palliative chemotherapy, decision priorities and information preferences. J Geriatr Oncol. 2020;11(4):626–32.
63. Macchini M, Chiaravalli M, Zanon S, Peretti U, Mazza E, Gianni L, et al. Chemotherapy in elderly patients with pancreatic cancer: efficacy, feasibility and future perspectives. Cancer Treat Rev. 2019;72:1–6.
64. Zijlstra M, van der Geest LGM, van Laarhoven HWM, Lemmens V, van de Poll-Franse LV, Raijmakers NJH. Patient characteristics and treatment considerations in pancreatic cancer: a population based study in the Netherlands. Acta Oncol. 2018;57(9):1185–91.
65. Tariman JD, Berry DL, Cochrane B, Doorenbos A, Schepp KG. Physician, patient, and contextual factors affecting treatment decisions in older adults with cancer and models of decision making: a literature review. Oncol Nurs Forum. 2012;39(1):E70–83.

Chapter 40
Surgery/Interventions in the Elderly Patient with Pancreatic Cancer

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Take Home Messages
- Older adults with pancreatic cancer can benefit from curative-intent surgery and surgery should not be denied on the basis of age alone.
- SBRT may be an appropriate treatment option for patients wishing to prioritize quality of life while maintaining favourable local control and median survival results.
- Comprehensive geriatric assessment is a structured assessment that identifies deficits, and also implements treatment plans for identified issues. This should be done by clinicians with geriatric expertise.

Pearls and Pitfalls
- Compared to geriatric-specific assessments, conventional measures of performance can miss modifiable deficits and poorly estimate treatment tolerance and outcomes.
- Geriatric screening tools can be used to identify those most likely to benefit from comprehensive geriatric assessment.

Future Perspectives
- Future studies are needed to evaluate how comprehensive geriatric assessment should guide oncologic treatment modifications, and the effect of treating identified deficits on oncologic treatments.

40.1 Introduction

Two-thirds of pancreatic cancers occur in adults 65 years and older; yet, older adults with pancreatic are underrepresented in clinical trials [1–5]. Data on long-term functional independence, quality of life, and avoiding prolonged recovery are scarce [6–9]. Complexity in decision-making arises with heterogeneity in underlying health status, life expectancy, and individual goals and preferences [10–12]. For these reasons, the understanding of how best to select or modify treatments is limited.

Traditionally, there is a bias towards undertreatment based on chronologic age, even in highly functional patients [13], whereby a minority of older adults undergo treatment, even in the absence of comorbidities [14–19]. Review at a multidisciplinary clinic with expertise in pancreatic cancer can increase the proportion receiving treatment [20]. Centralization into high-volume centres can also improve outcomes [21]. As a result, contemporary cancer care has seen a greater proportion of older adults with pancreatic cancer being treated without increasing complications [16, 17, 19, 22, 23].

In this chapter, the available evidence specifically relevant to older adults with pancreatic cancer is summarized.

40.2 Geriatric Considerations

Traditionally observed undertreatment has very recently improved with recognition that age alone inadequately describes older adults' diverse health statuses [24–26]. Tools to address the specificities of older adults' care have been refined. Conventional measures like ECOG (Eastern Cooperative Oncology Group) and Karnofsky performance statuses, ASA (American Society of Anesthesiologists) classification, and clinical judgement alone miss modifiable deficits and poorly estimate treatment tolerance and outcomes in older adults [27–32]. Geriatric-specific assessments and cancer care pathways have been developed to help patients and providers balance disease control and quality of life [33–38].

40.2.1 Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) is recommended [35–40]. CGA is conducted by multidisciplinary teams with geriatric expertise to evaluate physical health (comorbidities, medications, nutritional status), functional status, psychological status (cognitive and emotional), and socioeconomic factors (living situation, financial resources) [35, 41]. CGA can risk stratify patients, guide treatment decisions, and identify unrecognized health issues and geriatric syndromes [42–45]. CGA ultimately leads to a treatment plan for identified deficits to enable geriatric optimization and improve tolerance to treatment [38].

In older adults with pancreatic cancer, CGA identifies additional deficits in over 40% of patients previously selected for pancreatic surgery [46]. When CGA is used during multidisciplinary cancer conferences, 90% of older adults with resectable pancreatic cancer undergo surgery and 80% receive planned adjuvant chemotherapy, and it can support receipt of systemic therapy for unresectable or metastatic pancreatic cancer [47, 48]. Therefore, CGA can support decision-making to minimize under-treatment and support adaptation of care plans to individual patients, including potential unknown deficits. However, future studies are needed to evaluate how CGA should guide oncologic treatment modifications, how oncologic treatments impact CGA-domains, and the effect of treating CGA-identified deficits on oncologic treatments. A trial evaluating a CGA-stratified treatment approach is ongoing [49].

40.2.2 Geriatric Screening Tools

If resources are not available for all older adults to undergo CGA, geriatric screening tools can be used to select vulnerable older adults most likely to benefit from CGA [50–55]. This vulnerable state is referred to as frailty, which represents a state

of multisystem decline producing vulnerability to stressors with increased risk of poorer postoperative, functional, and oncologic outcomes [56, 57]. Many geriatric screening tools exist with variability in domains assessed and ease of use [50, 51]. The G8 and VES-13 (Vulnerable Elders Survey-13) are commonly used screening tools, completed in less than 5 min (Table 40.1); they are sensitive for CGA

Table 40.1 G8 tool [58]

Item	Answers	Points
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	Severe decrease in food intake	0
	Moderate decrease in food intake	1
	No decrease in food intake	2
Weight loss during the last 3 months	Weight loss >3 kg	0
	Does not know	1
	Weight loss between 1 and 3 kg	2
	No weight loss	3
Mobility	Bed or chair bound	0
	Able to get out of bed/ chair but does not go out	1
	Goes out	2
Neuropsychological problems	Severe dementia or depression	0
	Mild dementia or depression	1
	No psychological problems	2
Body mass index (BMI, kg/m^2)	<19	0
	19 to <21	1
	21 to <23	2
	≥23	3
Takes >3 medications per day	Yes	0
	No	1
In comparison to other people of the same age, how Does patient consider their health status?	Not as good	0
	Does not know	0.5
	As good	1
	Better	2
Age	>85	0
	80–85	1
	<80	2

- A score of ≤14 is abnormal (frail)

abnormalities and cancer treatment-related outcomes [58, 59]. VES-13 can be self-administered by patients. Multidisciplinary teams caring for patients with pancreatic cancer should select at least one tool to use routinely. This can be done by any trained team member. An abnormal screen should prompt referral for CGA [50–55].

40.2.3 Prehabilitation

Prehabilitation consists of planned processes intended to improve capacity to withstand upcoming stressors like surgery. The specific elements included in prehabilitation vary and are still undergoing investigation, but show promise [60–64]. Multi-modailty programs combining exercise and nutritional interventions and targeted by CGA are the most likely to be successful.

40.3 Surgery

40.3.1 Short-Term Outcomes

Short-term outcomes for older adults selected to undergo pancreaticoduodenectomy include 4.5% mortality, 47.2% morbidity, 18.6% pancreatic fistula, 2.6% biliary leak, 19.1% delayed gastric emptying, 7.3% postoperative hemorrhage, and 16.5% surgical site infection, as reported in mostly retrospective studies [65]. Population-level data indicated that outcomes for older adults have improved since the early 2000s, with 30-day mortality after any pancreatectomy going from 9.2% to 4.5% in the Netherlands [19], and reaching 6–7% in the U.S. [66–68]. Of note, pancreatectomy with venous resection for older adults does not yield worse outcomes [69, 70].

40.3.2 Oncologic Outcomes

The literature on oncologic outcomes after pancreatectomy for cancer in older adults is summarized in Table 40.2. Wide ranges exist in reported outcomes, with 5-year overall survival from 13% to 33% in population-based studies and from 10% to 41% in institution-based studies. All studies are retrospective and represent selected patients without clear reporting of the rationale for selection.

Table 40.2 Overall survival outcomes for older adults after resection

Study	Older adults (No.)	Age (years)	Data source	5-year overall survival, % (95% CI)
Studies using population-based or health administrative databases				
Lu 2018 [102]	1027	75+	SEER	24% (NR)[a]
He 2015 [16]	340	66+	Texas Cancer Registry-SEER-Medicare	25% (19–31%)
Van der Geest 2015 [19]	1472	70+	Netherlands Cancer Registry	13% (NR)
Turrini 2013 [103]	288	70–79	French Surgical Association	33% (NR)
Riall 2011 [66]	2393	66+	SEER-Medicare	35% (at 2 years)
Studies using institutional data				
Shamali 2017 [104]	102	75+	Single institution (United Kingdom)	35% (NR)
Futagawa 2017 [105]	81	75+	Single institution (Japan)	10% (NR)
Sho 2016 [106]	99	80+	Seven centres (Japan)	16% (NR)
Adham 2014 [107]	116	70+	Single institution (France)	41% (NR)
Oliveira-Cunha 2012 [108]	119	70+	Single institution (United Kingdom)	40% (NR)

Abbreviations: *CI* confidence interval; *SEER* Surveillance, Epidemiology, and End Results database; *No.* number; *NR* not reported; *NSQIP* American College of Surgeons National Surgical Quality Improvement Program

[a]Reporting disease-specific survival at 5-years without a competing risks approach

40.3.3 Patient-Centered and Geriatric-Relevant Outcomes

These outcomes for pancreatic cancer resection are reported in only one study. Quality of life in 70 older adults after pancreaticoduodenectomy improved most rapidly in the first 3 months after discharge [71]. While role functioning improved early, emotional functioning and fatigue improved more gradually over the first year [71]. Of note, preoperative quality of life was not assessed at baseline, and, thus, information on improvement or decline is not available. From a dependence perspective, recent data indicates that 5 years after pancreatectomy for cancer, 19.8% of older adults will become dependent on homecare services for personal support, and that 21.2% will survive while spending few days in institution each year [72].

40.3.4 Prognostic Factors for Surgical Outcomes

Information specific to older adults regarding prognostic factors following resection for pancreatic cancer remains limited [73]. Major prognostic factors reported are pre-operative frailty, which is associated with mortality and major

complications after pancreaticoduodenectomy [74], exhaustion and sarcopenia, which are associated with major morbidity [75], and the presence of CGA-deficits, which are associated with major morbidity and institutional discharge as previously mentioned [46].

40.3.5 Summary of the Surgical Literature

Overall, the understanding of surgery for pancreatic cancer in older adults remains limited, partly due to the low proportions of older adults undergoing surgery and the retrospective data hampered by selection bias. While favourable outcomes are reported, the criteria for selection for surgery are not known; selecting appropriate patients to achieve such outcomes relied mostly on individual surgeons' judgment. Therefore, it is challenging to use this information when assessing and counselling an individual patient in clinical practice. Additional information on patient-centered and geriatric-important outcomes are needed to guide individual risk-stratification and support decision-making from both a provider and patient perspective. In the interim, key prognostic factors specific to older adults can help, including frailty, exhaustion, sarcopenia, and CGA-deficits.

Older adults with pancreatic cancer can benefit from curative-intent surgery and surgery should not be denied on the basis of age alone. However, discussion regarding surgery requires a thorough discussion of risks and benefits, grounded by an objective assessment of patient values and geriatric-specific deficits. These decisions are best supported by objective measurements using CGA or geriatric-screening tools conducted prior to decision-making to limit undertreatment and optimize value-congruent care and outcomes.

40.4 Peri-Operative Systemic Treatment

40.4.1 Adjuvant Systemic Treatment

Retrospective studies have shown that among patients receiving adjuvant chemotherapy, patients 70 years and older have similar survival to younger patients, yet older adults are less likely to receive chemotherapy [76–78].

Overall, adjuvant single agent regimens are likely to be of benefit in older adults [79–82]. Combination regimens have increased toxicity and they require excellent performance status at baseline [83, 84]. Using CGA to select the regimen, or no systemic treatment, is likely the best approach, but no studies have investigated this to date.

40.4.2 Neoadjuvant Systemic Treatment

The evidence for neoadjuvant therapy (NAT) is evolving, and the best regimen is not yet defined. The information regarding older adults comes from two single-centered retrospective cohort studies [85, 86]. Overall, nearly half of older adults selected for NAT completed it as planned, with post-operative median survival from 20 to 34 months [85, 86]. No difference in NAT completion rates or median survival was observed when comparing to younger adults [85, 86]. Overall, the role of NAT for older adults is not yet well defined for resectable pancreas cancer.

40.4.3 Chemotherapy as an Alternative to Surgery

A retrospective cohort study using Surveillance, Epidemiology, and End Results (SEER)-Medicare data included 2629 older adults with resectable pancreas cancer treated with surgery or chemotherapy without surgery [87]. In unadjusted analysis, median overall survival was longer for patients treated with surgery compared to those receiving chemotherapy only (15 vs. 0 months). When adjusted for age, stage, sex, and comorbidities surgery still had a strong benefit. The magnitude of benefit in this study was only 3 months with surgery in those over 80 years, but was not substantially better in younger groups. There is little evidence to support the use of chemotherapy without surgery as a curative treatment for resectable pancreas cancer.

40.5 Radiotherapy

40.5.1 Adjuvant Concurrent Chemoradiation

The role of conventional concurrent chemoradiation remains controversial in all populations due to conflicting data from randomized clinical trials. The efficacy of concurrent chemoradiation for older adults is similar to the general population [88]. Overall, chemoradiation demonstrates the greatest survival with 5-year overall survival between 50% and 62%. Acute toxicity Grade III or higher is reported around 50%, but there is no information reported on late toxicity. However, these data come from retrospective studies with inherent selection bias, and information regarding health status or important geriatric baseline variables are not accounted for. As such, until further studies designed with these features in mind are done, careful patient selection is needed when deciding on adjuvant concurrent chemoradiation.

40.5.2 Stereotactic Body Radiation Therapy Without Surgery

Stereotactic body radiation therapy (SBRT) is an emerging modality which delivers ultra-high dose radiation in few fractions. Given no randomized comparison of SBRT to surgery in older adults, careful patient consideration and multidisciplinary evaluation is essential. Although SBRT is not curative in intent, it provides similar to better local control than conventionally delivered radiation with an improved toxicity profile [89]. In an early retrospective report of adults 80 years and older treated with SBRT, median local control was 11.5 months, with no Grade 3 toxicity reported and clinically relevant symptomatic improvement in pain in 80% [90]. A more recent retrospective single-arm cohort of patients felt to be not operative candidates based on non-standardized criteria and treated with SBRT reported median survival was 13 months, local progression-free survival at 1 year of 80%, and Grade 3 or higher toxicity of 10% [91]. Four retrospective single-arm cohort studies specifically included older adults treated with SBRT without surgery [92–95]. Across these four studies, median survival was 6–14 months, local control was 72–85% at 1 year and 63% at 2 years, and Grade 3 or higher toxicity of 0–15% [92–95]. Given the invasive nature and inherent risk of surgical resection, SBRT may be an appropriate treatment option for patients wishing to prioritize quality of life while maintaining favourable local control and median survival results.

40.5.3 Radiotherapy for Symptom Control

For patients requiring palliation of pain, radiotherapy should be considered. Short-course palliative radiotherapy is well tolerated and is associated with clinical response (complete pain control or decrease in use of analgesia) in 65–75% of patients treated [96–98]. The American Society for Radiation Oncology Clinical Practice Guideline gives a strong recommendation for the use of palliative radiation for symptom management [99]. Given its increased complexity of planning and delivery and potential risk of early and late toxicity, further studies are required to determine the role of SBRT specifically for palliation of pain. However, there is promise in SBRT as an option for palliation based upon a recent systematic review of SBRT demonstrated a global response to pain of 87% [100].

40.6 Integrating an Approach to Pancreatic Cancer in Older Adults

No comprehensive treatment pathways specific to older adults have been tested prospectively. In Fig. 40.1 we outline a framework to integrate geriatric principles with the available literature on surgical, systemic, and radiation treatments in a patient-centered way.

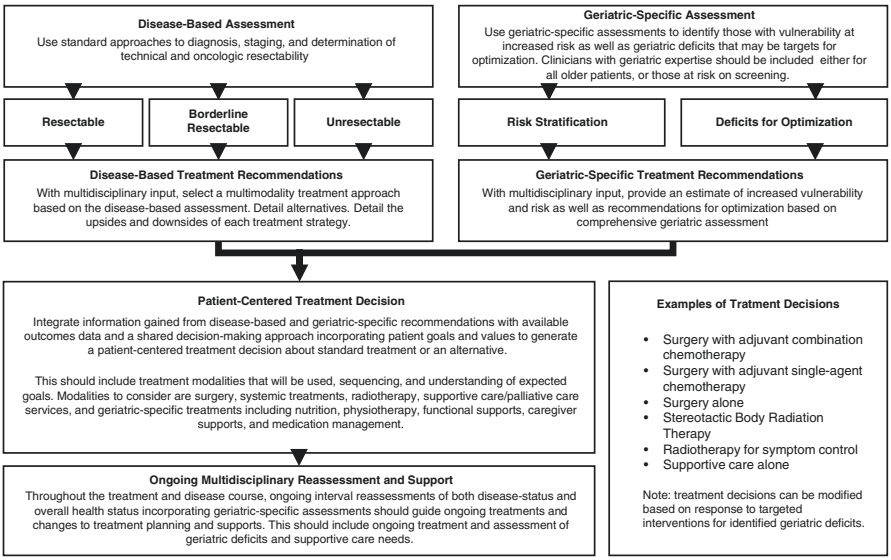

Fig. 40.1 Framework for the management of pancreatic cancer in older adults. Framework to integrate geriatric principles with the available literature on surgical, systemic, and radiation treatments in a patient-centered way. All older adults should be dually evaluated with a standard disease-based assessment and a geriatric-specific assessment. Integrate the information gained from both disease-based and geriatric-specific recommendations with the available outcomes data for surgical, systemic, and radiation treatments. Incorporate patient goals and values with using a shared-decision making approach to make a patient-centered treatment decision. Throughout the treatment and disease course, ongoing interval reassessments of both disease-status and overall health status incorporating geriatric-specific assessments should guide ongoing treatments and changes to treatment planning and supports

All older adults should be dually evaluated with a standard disease-based assessment and a geriatric-specific assessment. The disease-based assessment uses standard approaches to diagnosis and staging to determine technical and oncologic resectability. This disease-based assessment can generate a multimodal treatment recommendation specific to the pancreatic cancer, as well as alternative treatment approaches with their associated benefits and risks. Details of the standard approach to pancreatic cancer are detailed in other chapters of this textbook.

Geriatric-specific assessment aims to uncover otherwise overlooked vulnerability and deficits [27–38]. Ideally all patients undergo CGA; alternatively, geriatric screening tools can be used to select patients for referral for CGA [50–55]. While screening can be done by any trained person, CGA should be done by clinicians with geriatric expertise. The goals of geriatric-specific assessment are better risk stratification and identification of geriatric deficits for targeted optimization. Specific treatment and care process recommendations should then be made by the geriatric team to target identified geriatric-deficits by clinicians with geriatric expertise [38].

Counselling and decision-making can then be guided by integrating the information gained from both disease-based and geriatric-specific assessments. It is

important to elicit and incorporate patient goals and values to make a patient-centered treatment decision [101]. Addressing CGA-deficits may optimize oncologic treatment tolerance and benefit, and mitigate harms [42–45]. The integrated patient-centred treatment decision should detail (1) treatment modalities, (2) sequencing, (3) expected goals, and (4) events triggering change in plans. Modalities to consider are surgery, systemic treatments, radiotherapy, supportive and palliative services, and geriatric-directed treatments such as nutrition, physiotherapy, functional supports, caregiver supports, and medication management. Finally, both disease-status and performance-status should be routinely reassessed throughout the treatment and disease course to guide changes to care plans and supportive care.

40.7 Conclusions

The proportion of older adults with pancreatic cancer receiving treatment has improved over the past decades with the recognition that age alone should not determine treatments. Objective assessments of performance and potential deficits are crucial to tailor treatment to older adults, avoid undertreatment, and align therapy with patients' wishes and values. Concurrent multidisciplinary disease-based and geriatric-specific assessments should guide patient-centered treatment decisions. Involving clinicians with geriatric expertise is critical to improve risk stratification, uncover unrecognized health issues and geriatric syndromes, and target geriatric deficits to optimize oncologic treatment benefit and mitigate harms.

Finally, studies addressing the specific needs of older adults with pancreatic cancer are still needed. Additional information is warranted to truly individualize counselling and decision-making, including data pertaining to geriatric-relevant baseline characteristics, selection criteria for chosen treatments currently used, and long-term dependence outcomes most relevant to older adults. Ultimately, robustly developed and externally validated prediction models for individualized risk assessments may support clinical practice and allow for an evaluation of treatment approaches tailored to individual risk.

References

1. Howlader N, Noone A, Krapcho M, et al. SEER cancer statistics review, 1975–2016. Pancreatic cancer SEER 21 2012–2016, all races, both sexes. Natl. Cancer Inst. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed 9 Sept 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
3. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV, Cohen HJ, Muss HB, Schilsky RL, Ferrell B, Extermann M. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32:2587.
4. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol. 2005;23:3112–24.

5. White MN, Dotan E, Catalano PJ, Cardin DB, Berlin JD. Advanced pancreatic cancer clinical trials: the continued underrepresentation of older patients. J Geriatr Oncol. 2018;10(4):540–6.
6. Fried TR, Van Ness PH, Byers AL, Towle VR, O'Leary JR, Dubin JA. Changes in preferences for life-sustaining treatment among older persons with advanced illness. J Gen Intern Med. 2007;22:495–501.
7. Barnato AE, Herndon MB, Anthony DL, Gallagher PM, Skinner JS, Bynum JPW, Fisher ES. Are regional variations in end-of-life care intensity explained by patient preferences?: a study of the US Medicare population. Med Care. 2007;45:386.
8. Teno JM, Fisher ES, Hamel MB, Coppola K, Dawson NV. Medical care inconsistent with patients' treatment goals: association with 1-year Medicare resource use and survival. J Am Geriatr Soc. 2002;50:496–500.
9. Nabozny MJ, Kruser JM, Steffens NM, Brasel KJ, Campbell TC, Gaines ME, Schwarze ML. Constructing high-stakes surgical decisions: it's better to die trying. Ann Surg. 2016;263:64.
10. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. JAMA. 2012;307:182–92.
11. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341:2061–7.
12. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004;22:4626–31.
13. Foster JA, Salinas GD, Mansell D, Williamson JC, Casebeer LL. How does older age influence oncologists' cancer management? Oncologist. 2010;15:584–92.
14. Amin S, Lucas AL, Frucht H. Evidence for treatment and survival disparities by age in pancreatic adenocarcinoma: a population-based analysis. Pancreas. 2013;42:249.
15. Sehgal R, Alsharedi M, Larck C, Edwards P, Gress T. Pancreatic cancer survival in elderly patients treated with chemotherapy. Pancreas. 2014;43:306–10.
16. He W, Zhao H, Chan W, Lopez D, Shroff RT, Giordano SH. Underuse of surgical resection among elderly patients with early-stage pancreatic cancer. Surgery. 2015;158:1226–34.
17. van der Geest LGM, Haj Mohammad N, Besselink MGH, Lemmens VEPP, Portielje JEA, van Laarhoven HWM, Wilmink JW, Group DPC. Nationwide trends in chemotherapy use and survival of elderly patients with metastatic pancreatic cancer. Cancer Med. 2017;6:2840–9.
18. Mavros MN, Coburn NG, Davis LE, Mahar AL, Liu Y, Beyfuss K, Myrehaug S, Earle CC, Hallet J. Low rates of specialized cancer consultation and cancer-directed therapy for noncurable pancreatic adenocarcinoma: a population-based analysis. CMAJ. 2019;191:E574–80.
19. van der Geest LGM, Besselink MGH, van Gestel YRBM, Busch ORC, de Hingh IHJT, de Jong KP, Molenaar IQ, Lemmens VEPP. Pancreatic cancer surgery in elderly patients: balancing between short-term harm and long-term benefit. A population-based study in the Netherlands. Acta Oncol (Madr). 2016;55:278–85.
20. King JC, Zenati M, Steve J, Winters SB, Bartlett DL, Zureikat AH, Zeh HJ, Hogg ME. Deviations from expected treatment of pancreatic cancer in octogenarians: analysis of patient and surgeon factors. Ann Surg Oncol. 2016;23:4149–55.
21. Gooiker GA, van Gijn W, Wouters MWJM, Post PN, Van De Velde CJH, Tollenaar R, Society SCC of the DC. Systematic review and meta-analysis of the volume–outcome relationship in pancreatic surgery. Br J Surg. 2011;98:485–94.
22. van der Geest LGM, Besselink MGH, Busch ORC, de Hingh IHJT, van Eijck CHJ, Dejong CHC, Lemmens VEPP. Elderly patients strongly benefit from centralization of pancreatic cancer surgery: a population-based study. Ann Surg Oncol. 2016;23:2002–9.
23. Neuwirth MG, Bierema C, Sinnamon AJ, Fraker DL, Kelz RR, Roses RE, Karakousis GC. Trends in major upper abdominal surgery for cancer in octogenarians: has there been a change in patient selection? Cancer. 2018;124:125–35.
24. Lowsky DJ, Olshansky SJ, Bhattacharya J, Goldman DP. Heterogeneity in healthy aging. J Gerontol Ser A Biomed Sci Med Sci. 2013;69:640–9.

25. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, Curigliano G, Extermann M, Lichtman SM, Ballman K. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology position article. J Clin Oncol. 2013;31:3711–8.
26. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol. 2018;19:e305–16.
27. Robinson TN, Eiseman B, Wallace JI, Church SD, McFann KK, Pfister SM, Sharp TJ, Moss M. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg. 2009;250:449–55.
28. Jolly TA, Deal AM, Nyrop KA, Williams GR, Pergolotti M, Wood WA, Alston SM, Gordon B-BE, Dixon SA, Moore SG. Geriatric assessment-identified deficits in older cancer patients with normal performance status. Oncologist. 2015;20:379–85.
29. Kirkhus L, Benth JŠ, Rostoft S, Grønberg BH, Hjermstad MJ, Selbæk G, Wyller TB, Harneshaug M, Jordhøy MS. Geriatric assessment is superior to oncologists' clinical judgement in identifying frailty. Br J Cancer. 2017;117:470.
30. Revenig LM, Canter DJ, Henderson MA, Ogan K, Kooby DA, Maithel SK, Liu Y, Kim S, Master VA. Preoperative quantification of perceptions of surgical frailty. J Surg Res. 2015;193:583–9.
31. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210:901–8.
32. Sacks GD, Dawes AJ, Ettner SL, Brook RH, Fox CR, Maggard-Gibbons M, Ko CY, Russell MM. Surgeon perception of risk and benefit in the decision to operate. Ann Surg. 2016;264:896–903.
33. Shahrokni A, Kim SJ, Bosl GJ, Korc-Grodzicki B. How we care for an older patient with cancer. J Oncol Pract. 2017;13:95–102.
34. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg. 2012;215:453–66.
35. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, Falandry C, Artz A, Brain E, Colloca G. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595.
36. National Comprehensive Cancer Network Older Adult Oncology (Version 2.2018). https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf. Accessed 19 Oct 2018.
37. Aapro M, Schrijvers D. ESMO handbook of cancer in the senior patient, ESMO handbook series. 2nd ed. Lugano: ESMO; 2015.
38. Mohile SG, Velarde C, Hurria A, Magnuson A, Lowenstein L, Pandya C, O'Donovan A, Gorawara-Bhat R, Dale W. Geriatric assessment-guided care processes for older adults: a Delphi consensus of geriatric oncology experts. J Natl Compr Canc Netw. 2015;13:1120–30.
39. Pallis AG, Ring A, Fortpied C, Penninckx B, Van Nes MC, Wedding U, Vonminckwitz G, Johnson CD, Wyld L, Timmer-Bonte A. EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22:1922–6.
40. Pallis AG, Fortpied C, Wedding U, Van Nes MC, Penninckx B, Ring A, Lacombe D, Monfardini S, Scalliet P, Wildiers H. EORTC elderly task force position paper: approach to the older cancer patient. Eur J Cancer. 2010;46:1502–13.
41. Puts MTE, Alibhai SMH. Fighting back against the dilution of the comprehensive geriatric assessment. J Geriatr Oncol. 2018;9:3–5.
42. Caillet P, Laurent M, Bastuji-Garin S, Liuu E, Culine S, Lagrange J-L, Canoui-Poitrine F, Paillaud E. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging. 2014;9:1645.

43. Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - a systematic review. J Geriatr Oncol. 2018;9:430–40.
44. Kim K, Park K-H, Koo K-H, Han H-S, Kim C-H. Comprehensive geriatric assessment can predict postoperative morbidity and mortality in elderly patients undergoing elective surgery. Arch Gerontol Geriatr. 2013;56:507–12.
45. Kalsi T, Babic-Illman G, Ross PJ, Maisey NR, Hughes S, Fields P, Martin FC, Wang Y, Harari D. The impact of comprehensive geriatric assessment interventions on tolerance to chemotherapy in older people. Br J Cancer. 2015;112:1435.
46. Dale W, Hemmerich J, Kamm A, Posner MC, Matthews JB, Rothman R, Palakodeti A, Roggin KK. Geriatric assessment improves prediction of surgical outcomes in older adults undergoing pancreaticoduodenectomy: a prospective cohort study. Ann Surg. 2014;259:960–5.
47. Castel-Kremer E, De Talhouet S, Charlois A-L, Graillot E, Chopin-Laly X, Adham M, Comte B, Lombard-Bohas C, Walter T, Boschetti G. An onco-geriatric approach to select older patients for optimal treatments of pancreatic adenocarcinoma. J Geriatr Oncol. 2018;9:373–81.
48. Tudini M, Palluzzi E, Cannita K, Mancini M, Santomaggio A, Bruera G, Baldi PL, Pelliccione M, Ricevuto E, Ficorella C. Modulation of GemOx chemotherapy according to CIRS in elderly patients with advanced pancreatic cancer. Oncol Rep. 2012;27:423–32.
49. Betge J, Chi-Kern J, Schulte N, Belle S, Gutting T, Burgermeister E, Jesenofsky R, Maenz M, Wedding U, Ebert MP. A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine+/− nab-paclitaxel in elderly pancreatic cancer patients (GrantPax). BMC Cancer. 2018;18:747.
50. Loh KP, Soto-Perez-de-Celis E, Hsu T, de Glas NA, Battisti NML, Baldini C, Rodrigues M, Lichtman SM, Wildiers H. What every oncologist should know about geriatric assessment for older patients with cancer: Young International Society of Geriatric Oncology position paper. J Oncol Pract. 2018;14:85–94.
51. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, Rostoft S, Overcash J, Wildiers H, Steer C. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. Ann Oncol. 2014;26:288–300.
52. Hall DE, Arya S, Schmid KK, Carlson MA, Lavedan P, Bailey TL, Purviance G, Bockman T, Lynch TG, Johanning JM. Association of a frailty screening initiative with postoperative survival at 30, 180, and 365 days. JAMA Surg. 2017;152:233–40.
53. Alvarez-Nebreda ML, Bentov N, Urman RD, Setia S, Huang JC-S, Pfeifer K, Bennett K, Ong TD, Richman D, Gollapudi D. Recommendations for preoperative management of frailty from the Society for Perioperative Assessment and Quality Improvement (SPAQI). J Clin Anesth. 2018;47:33–42.
54. Magnuson A, Canin B, van Londen GJ, Edwards B, Bakalarski P, Parker I. Incorporating geriatric medicine providers into the care of the older adult with cancer. Curr Oncol Rep. 2016;18:65.
55. McDonald SR, Heflin MT, Whitson HE, Dalton TO, Lidsky ME, Liu P, Poer CM, Sloane R, Thacker JK, White HK. Association of integrated care coordination with postsurgical outcomes in high-risk older adults: the Perioperative Optimization of Senior Health (POSH) initiative. JAMA Surg. 2018;153:454–62.
56. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752–62.
57. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin. 2017;67:362–77.
58. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, Soubeyran PL. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23:2166–72.

59. Yokom DW, Alibhai SMH, Sattar S, Krzyzanowska MK, Puts MTE. Geriatric oncology screening tools for CGA-based interventions: results from a phase II study of geriatric assessment and management for older adults with cancer. J Geriatr Oncol. 2018;9(6):683–6.
60. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, Momblán D, Balust J, Blanco I, Martínez-Pallí G. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg. 2018;267:50–6.
61. Luther A, Gabriel J, Watson RP, Francis NK. The impact of total body prehabilitation on post-operative outcomes after major abdominal surgery: a systematic review. World J Surg. 2018; https://doi.org/10.1007/s00268-018-4569-y.
62. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, Sajobi TT, Fenton TR. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology. 2018;155(2):391–410.e4.
63. Stephensen D, Hashem F, Corbett K, Bates A, George M, Hobbs RP, Hopkins M, Hutchins I, Lowery DP, Pellatt-Higgins T. Effects of preoperative and postoperative resistance exercise interventions on recovery of physical function in patients undergoing abdominal surgery for cancer: a systematic review of randomised controlled trials. BMJ Open Sport Exerc Med. 2018;4:e000331.
64. Vermillion SA, James A, Dorrell RD, Brubaker P, Mihalko SL, Hill AR, Clark CJ. Preoperative exercise therapy for gastrointestinal cancer patients: a systematic review. Syst Rev. 2018;7:103.
65. Pędziwiatr M, Małczak P, Mizera M, Witowski J, Torbicz G, Major P, Pisarska M, Wysocki M, Jankowski M, Rubinkiewicz M. Pancreatoduodenectomy for pancreatic head tumors in the elderly–systematic review and meta-analysis. Surg Oncol. 2018;27(3):346–64.
66. Riall TS, Sheffield KM, Kuo Y, Townsend CM Jr, Goodwin JS. Resection benefits older adults with locoregional pancreatic cancer despite greater short-term morbidity and mortality. J Am Geriatr Soc. 2011;59:647–54.
67. Lee DY, Schwartz JA, Wexelman B, Kirchoff D, Yang KC, Attiyeh F. Outcomes of pancreaticoduodenectomy for pancreatic malignancy in octogenarians: an American College of Surgeons National Surgical Quality Improvement Program analysis. Am J Surg. 2014;207:540–8.
68. Nayar P, Chandak A, Yu F, Sayles H, Ganti AK. Mortality following pancreatectomy for elderly rural veterans with pancreatic cancer. J Geriatr Oncol. 2017;8:284–8.
69. Kanda M, Fujii T, Suenaga M, Takami H, Inokawa Y, Yamada S, Kobayashi D, Tanaka C, Sugimoto H, Nomoto S. Pancreatoduodenectomy with portal vein resection is feasible and potentially beneficial for elderly patients with pancreatic cancer. Pancreas. 2014;43:951–8.
70. Fang J-Z, Lu C-D, Wu S-D, Huang J, Zhou J. Portal vein/superior mesenteric vein resection in pancreatic cancer treatment in the elderly. Medicine (Baltimore). 2017;96:e7335.
71. Gerstenhaber F, Grossman J, Lubezky N, Itzkowitz E, Nachmany I, Sever R, Ben-Haim M, Nakache R, Klausner JM, Lahat G. Pancreaticoduodenectomy in elderly adults: is it justified in terms of mortality, long-term morbidity, and quality of life? J Am Geriatr Soc. 2013;61:1351–7.
72. Bennett S, Chesney T, Coburn N, et al. Long-term dependency outcomes in older adults following hepatectomy and pancreatectomy for cancer: a population-based analysis. HPB. 2020;22(10):S31–S32
73. Riley RD, Hayden JA, Steyerberg EW, Moons KGM, Abrams K, Kyzas PA, Malats N, Briggs A, Schroter S, Altman DG. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS Med. 2013;10:e1001380.
74. Augustin T, Burstein MD, Schneider EB, Morris-Stiff G, Wey J, Chalikonda S, Walsh RM. Frailty predicts risk of life-threatening complications and mortality after pancreatic resections. Surgery. 2016;160:987–96.
75. Sur MD, Namm JP, Hemmerich JA, Buschmann MM, Roggin KK, Dale W. Radiographic sarcopenia and self-reported exhaustion independently predict NSQIP serious complications after pancreaticoduodenectomy in older adults. Ann Surg Oncol. 2015;22:3897–904.

76. Shin SH, Park Y, Hwang DW, Song KB, Lee JH, Kwon J, Yoo C, Alshammary S, Kim SC. Prognostic value of adjuvant chemotherapy following pancreaticoduodenectomy in elderly patients with pancreatic cancer. Anticancer Res. 2019;39:1005–12.
77. Nagrial AM, Chang DK, Nguyen NQ, Johns AL, Chantrill LA, Humphris JL, Chin VT, Samra JS, Gill AJ, Pajic M. Adjuvant chemotherapy in elderly patients with pancreatic cancer. Br J Cancer. 2014;110:313.
78. Watanabe Y, Shinkawa T, Endo S, Abe Y, Nishihara K, Nakano T. Long-term outcomes after pancreatectomy for pancreatic ductal adenocarcinoma in elderly patients: special reference to postoperative adjuvant chemotherapy. World J Surg. 2018;42:2617–26.
79. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358:1576–85.
80. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200–10.
81. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304:1073–81.
82. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310:1473–81.
83. Neoptolemos JP, Palmer D, Ghaneh P, Valle J, Cunningham D, Wadsley J, Meyer T, Anthoney A, Glimelius B, Falk S. ESPAC-4: a multicenter, international, randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma. Pancreas. 2016;45:1529.
84. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul J-L, Choné L, Francois E, Artru P, Biagi JJ. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395–406.
85. Miura JT, Krepline AN, George B, Ritch PS, Erickson BA, Johnston FM, Oshima K, Christians KK, Evans DB, Tsai S. Use of neoadjuvant therapy in patients 75 years of age and older with pancreatic cancer. Surgery. 2015;158:1545–55.
86. Cooper AB, Holmes HM, Des Bordes JKA, Fogelman D, Parker NH, Lee JE, Aloia TA, Vauthey J-N, Fleming JB, Katz MHG. Role of neoadjuvant therapy in the multimodality treatment of older patients with pancreatic cancer. J Am Coll Surg. 2014;219:111–20.
87. Marmor S, Burke EE, Virnig BA, Jensen EH, Tuttle TM. A comparative analysis of survival outcomes between pancreatectomy and chemotherapy for elderly patients with adenocarcinoma of the pancreas. Cancer. 2016;122:3378–85.
88. Ciabatti S, Cammelli S, Frakulli R, Arcelli A, Macchia G, Deodato F, Cilla S, Giaccherini L, Buwenge M, Morganti AG. Radiotherapy of pancreatic cancer in older patients: a systematic review. J Geriatr Oncol. 2019;10:534–9.
89. Zhong J, Patel K, Switchenko J, Cassidy RJ, Hall WA, Gillespie T, Patel PR, Kooby D, Landry J. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. Cancer. 2017;123:3486–93.
90. Kim CH, Ling DC, Wegner RE, Flickinger JC, Heron DE, Zeh H, Moser AJ, Burton SA. Stereotactic body radiotherapy in the treatment of pancreatic adenocarcinoma in elderly patients. Radiat Oncol. 2013;8:240.
91. Ryan JF, Rosati LM, Groot VP, Le DT, Zheng L, Laheru DA, Shin EJ, Jackson J, Moore J, Narang AK. Stereotactic body radiation therapy for palliative management of pancreatic adenocarcinoma in elderly and medically inoperable patients. Oncotarget. 2018;9:16427.

92. Scorsetti M, Clerici E, Navarria P, D'Agostino G, Piergallini L, De Rose F, Ascolese A, Tozzi A, Iftode C, Villa E. The role of stereotactic body radiation therapy (SBRT) in the treatment of oligometastatic disease in the elderly. Br J Radiol. 2015;88:20150111.
93. Zhu X, Li F, Ju X, Cao F, Cao Y, Fang F, Qing S, Shen Y, Jia Z, Zhang H. Prognostic role of stereotactic body radiation therapy for elderly patients with advanced and medically inoperable pancreatic cancer. Cancer Med. 2017;6:2263–70.
94. Yechieli RL, Robbins JR, Mahan M, Siddiqui F, Ajlouni M. Stereotactic body radiotherapy for elderly patients with medically inoperable pancreatic cancer. Am J Clin Oncol. 2017;40:22–6.
95. Sutera PA, Bernard M, Wang H, Heron DE. Prognostic factors for elderly patients treated with stereotactic body radiation therapy for pancreatic adenocarcinoma. Front Oncol. 2018;8:282.
96. Ebrahimi G, Rasch CRN, van Tienhoven G. Pain relief after a short course of palliative radiotherapy in pancreatic cancer, the Academic Medical Center (AMC) experience. Acta Oncol (Madr). 2018;57:697–700.
97. Morganti AG, Trodella L, Valentini V, Barbi S, Macchia G, Mantini G, Turriziani A, Cellini N. Pain relief with short term irradiation in locally advanced carcinoma of the pancreas. J Palliat Care. 2003;19:258–62.
98. Wolny-Rokicka E, Sutkowski K, Grządziel A, Dorsz Ż, Tukiendorf A, Lipiński J, Wydmański J. Tolerance and efficacy of palliative radiotherapy for advanced pancreatic cancer: a retrospective analysis of single-institutional experiences. Mol Clin Oncol. 2016;4:1088–92.
99. Palta M, Godfrey D, Goodman KA, Hoffe S, Dawson LA, Dessert D, Hall WA, Herman JM, Khorana AA, Merchant N. Radiation therapy for pancreatic cancer: executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol. 2019;9:322–32.
100. Buwenge M, Macchia G, Arcelli A, Frakulli R, Fuccio L, Guerri S, Grassi E, Cammelli S, Cellini F, Morganti AG. Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. J Pain Res. 2018;11:2169.
101. Chesney TR, Schwarze ML. Patient-centered surgical decision making. In: Rosenthal R, Zenilman M, Katlic M, editors. Princ. Pract. Geriatr. Surg. 3rd ed. New York: Springer; 2017. p. 1–13.
102. Lu L, Zhang X, Tang G, Shang Y, Liu P, Wei Y, Gong P, Ma L. Pancreaticoduodenectomy is justified in a subset of elderly patients with pancreatic ductal adenocarcinoma: a population-based retrospective cohort study of 4283 patients. Int J Surg. 2018;53:262–8.
103. Turrini O, Paye F, Bachellier P, Sauvanet A, Cunha AS, Le Treut YP, Adham M, Mabrut JY, Chiche L, Delpero JR. Pancreatectomy for adenocarcinoma in elderly patients: postoperative outcomes and long term results: a study of the French Surgical Association. Eur J Surg Oncol. 2013;39:171–8.
104. Shamali A, De'Ath HD, Jaber B, Abuawad M, Barbaro S, Hamaday Z, Hilal MA. Elderly patients have similar short term outcomes and five-year survival compared to younger patients after pancreaticoduodenectomy. Int J Surg. 2017;45:138–43.
105. Futagawa Y, Kanehira M, Furukawa K, Kitamura H, Yoshida S, Usuba T, Misawa T, Ishida Y, Okamoto T, Yanaga K. Study on the validity of pancreaticoduodenectomy in the elderly. Anticancer Res. 2017;37:5309–16.
106. Sho M, Murakami Y, Kawai M, Motoi F, Satoi S, Matsumoto I, Honda G, Uemura K, Yanagimoto H, Kurata M. Prognosis after surgical treatment for pancreatic cancer in patients aged 80 years or older: a multicenter study. J Hepatobiliary Pancreat Sci. 2016;23:188–97.
107. Adham M, Bredt LC, Robert M, Perinel J, Lombard-Bohas C, Ponchon T, Valette PJ. Pancreatic resection in elderly patients: should it be denied? Langenbecks Arch Surg. 2014;399:449–59.
108. Oliveira-Cunha M, Malde DJ, Aldouri A, Morris-Stiff G, Menon KV, Smith AM. Results of pancreatic surgery in the elderly: is age a barrier? HPB. 2013;15:24–30.

Chapter 41
Preoperative Management of Jaundice

Savio George Barreto and John A. Windsor

Take Home Messages

- There is no role for routine preoperative biliary drainage in pancreatic head cancer. The indications for selective preoperative biliary drainage include presence of cholangitis, need for neoadjuvant chemotherapy, a delay to surgery and a bilirubin level of ≥15 mg/dL. The decision must take into account the availability of facilities and expertise in the performance of ERCP or PTBD. Prophylactic antibiotics are indicated prior to drainage. The most widely preferred approach to drainage is endoscopic SEMS and there should be a delay of 4–6 weeks until surgery.

Pearls and Pitfalls

- While SEMS are preferred, especially in locally advanced pancreatic cancer, they need to be removed prior to irreversible electroporation (IRE).

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Future Perspectives

- There is a need for development of unified guidelines on the indications for preoperative biliary drainage in pancreatic cancer specifically addressing the need for drainage (or lack of it) and timing, when indicated. There is sufficient evidence to guide the choice of stent used, as well.
- With the increasing use of irreversible electroporation (IRE) and radiofrequency ablation (RFA), the use of SEMS, their safety, and need for removal must be clearly elucidated.

41.1 Introduction

Obstructive jaundice in patients over 40 years old is associated with a 4% risk of pancreatic cancer, but only 30% of patients with pancreatic cancer present with it [1]. This figure rises up to 81% in patients with cancer of the pancreatic head (Fig. 41.1a) [2]. Obstructive jaundice is a negative risk factor affecting overall survival in pancreatic cancer patients undergoing resection [2].

The management of obstructive jaundice in pancreatic head cancer has evolved tremendously over the last century. This chapter provides a detailed discussion, based on available evidence, for the management of obstructive jaundice in patients with pancreatic head cancer.

41.2 Historical Perspective

Obstructive jaundice has long been recognized as a key presenting symptom of pancreatic head cancer. While an understanding of the role of Vitamin K in the pathophysiology of obstructive jaundice is more recent, early surgeons made the

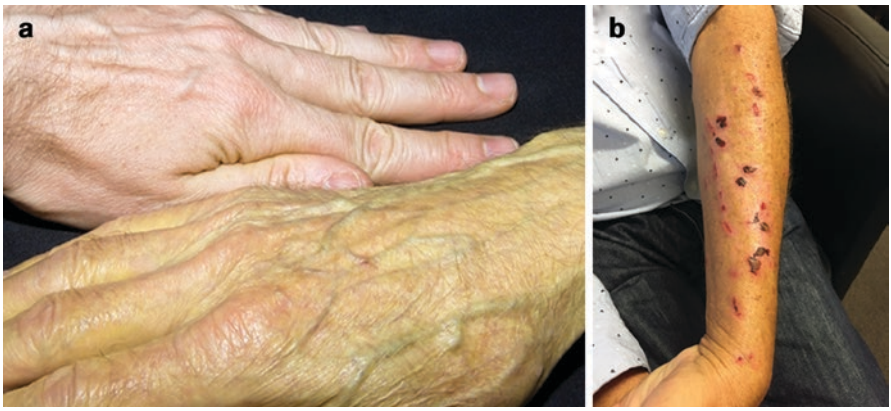

Fig. 41.1 Clinical images: (**a**) patient with jaundice, (**b**) Cutaneous abrasions secondary to scratching as a result of pruritis from obstructive jaundice

link between obstructive jaundice (or what they referred to as 'cholemia') and the risk of bleeding during pancreatic cancer surgery. The first attempts to directly treat the obstructive jaundice was done by open tube cholecystostomy. It was Dr. Monastyrski, a Russian surgeon, [3] who argued that cholecystostomy carried a high risk of peritonitis and while it would eliminate 'cholemia', it resulted in patients wasting away and dying with continuing loss of bile. He performed the first cholecystojejunostomy, or internal biliary drainage, for a pancreatic tumour in 1887 [3]. During the ensuing decades, numerous approaches to biliary drainage were promoted, including the use of cholecysto-jejunal anastomosis [4, 5], the use of a rubber tubing to drain the common bile duct into the duodenum [6], bilio-enteric anastomosis using the cystic duct after ligating the distal common bile duct [7], choledochoduodenostomy [8], and cholecystogastrostomy [9].

By the 1960s, retrospective reports began to emerge of successful percutaneous transhepatic biliary drainage (PTBD) in managing obstructive jaundice [10–12]. However, prospective controlled trials (comparing PTBD followed by laparotomy to up-front laparotomy) not only failed to demonstrate the benefit of PTBD, but even suggested worse outcomes due to an increased rate of complications [13, 14] and cost [15] from the procedure.

By the 1970s there were reports of preoperative endoscopic retrograde cholangiopancreatography (ERCP) and the placement of internal stents or nasobiliary drains to relieve obstructive jaundice [16–18]. This was found to be more effective and associated with lower mortality rates when compared with PTBD [19]. ERCP and biliary drainage rapidly became the preferred approach to relieving jaundice, in part because it was less invasive and did not leave a patient with an external drain [20]. Over time and with increasing experience there began to emerge reports of adverse outcomes with endoscopic biliary drainage [21, 22]. PTBD has specific indications, including following failed ERCP, and can be used to facilitate successful ERCP by the rendezvous technique. This involves the prior insertion of a percutaneous transhepatic wire through to the duodenum, over which a stent can be inserted through the ampullary into the bile duct.

41.3 Aetiology of Obstructive Jaundice in Pancreatic Cancer

The most common cause of obstructive jaundice in pancreatic head cancer is the occlusion of the distal common bile duct by the cicatrizing tumour. Less common causes include extrinsic compression of the bile duct by pathologically enlarged portal lymph nodes or liver metastases. The extent of liver dysfunction from metastases varies from mild cholestasis with obstruction of peripheral intrahepatic bile ducts, through to liver failure from centrally placed liver metastases obstructing right and left hepatic ducts [23]. This indicates that obstructive jaundice in the context of pancreatic head cancer cannot always be relieved by biliary drainage.

41.3.1 Clinical Features

In terms of clinical signs, obstructive jaundice leads to scleral icterus when the serum bilirubin level exceeds 3 mg/dL. Patients often report the passage of dark urine (as a result of increased levels of water-soluble bilirubin) and pale stools (due to the lack of stercobilin). On examination of the abdomen, patients with a malignant obstruction of the distal bile duct are likely to have a palpable gallbladder (Courvoisier's sign). In contrast, obstructive jaundice due to choledocholithiasis is associated with chronic inflammation of the gallbladder wall (with gallstones), and does not readily distend.

Unrelieved obstructive jaundice is often associated with pruritus but the level of serum bilirubin does correlated with severity of pruritis [24]. There appears to be a role for histamine release from subcutaneous mast cells in response to the increased bile salt levels. And there is increasing evidence for a central pathway for the cause of pruritis, mediated by serotonin, steroids, endogenous opioids, and lysophosphatidic acid [25]. Intractable pruritis is very distressing and leads to injury to the skin (including abrasions, wounds and scabs) (Fig. 41.1b) and superficial bruising (ecchymosis) because of the associated coagulopathy (Box 41.2). The principles for treating pruritis are covered in Box 41.1 [25].

Box 41.1 Principles of Treatment of Pruritis-Secondary to Obstructive Jaundice

Biliary drainage

- ERCP and stent (plastic or SEMS)
- PTBD
- Rendezvous procedure

Supportive measures

- Bathing in cool or tepid water
- Topical oil-based moisturisers and emollients (e.g. Calamine)
- Avoid soap and skin irritants
- Hydration (>2 L of oral fluids per day)

Specific medications

- Anti-histamines
- Ursodeoxycholic acid (10–15 mg/kg/day orally)
- Anion exchange resins (e.g. Cholestyramine, 4–16 g/day orally)
- Opioid antagonists (e.g. Naltrexone, 50 mg/day orally)
- Serotonin antagonists (e.g. Sertraline, 100 mg/day orally)
- Rifampicin (300–600 mg/day orally)

41.4 Consequences of Obstructive Jaundice

Patients with obstructive jaundice have an increased risk of wound complications, including infection, delayed healing, dehiscence and herniae [26]. The reduction in the levels of propylhydroxylase, an enzyme required for the incorporation of the amino acid proline into cutaneous collagen, may be the reason for reduced wound strength [26]. Obstructive jaundice also results in delayed wound healing and dehiscence, possibly due to the effects of endotoxins (caused by increased intestinal translocation from lack of bile in the gut lumen and a decreased clearance by Kupfer cells) on fibroblasts and to protein malnutrition, a common finding in patients with pancreatic head cancer [27].

Experimental and clinical evidence [28] indicates that obstructive jaundice has multiple consequences including an impaired intestinal barrier function and increased intestinal permeability (facilitating bacterial translocation), altered mucosal immunity and reticuloendothelial function. It also causes a reduction in the number and function of gut mucosal T lymphocytes as well as impairs cell-mediated immunity. There is direct liver injury with an attendant decrease in Kupffer cell function with resultant endotoxemia (high TNF and IL-6 levels). Besides, obstructive jaundice affects the functioning of other organ systems such as the cardiovascular and renal systems (Fig. 41.2).

Hepatorenal syndrome, defined as a reversible renal impairment secondary to liver disease and is characterized by marked reduction in glomerular filtration rate (GFR) and renal plasma flow. It is diagnosed when no cause of renal failure has been identified, and rarely occurs in association with obstructive jaundice. It is more likely to occur in the presence of cirrhosis, hypotension/hypovolaemia and following major surgery. Although acute kidney failure is found in only 10% of patients with obstructive jaundice, it is associated with a high mortality risk [27]. This concern was one of the reasons widely cited for mandatory preoperative biliary drainage.

Malnutrition and coagulopathy in obstructive jaundice result from malabsorption of fats (causing steatorrhoea) and fat-soluble vitamins (i.e. A, D, E and K) as well as liver dysfunction (metabolic and synthetic capacity) and the resultant reduction in protein synthesis, gluconeogenesis, and disordered ketogenesis [29, 30]. Nutritional optimisation is important in this cohort of patients. Cachexia of cancer leads to poor outcomes perioperatively as well as in terms of survival [31]. Early involvement of the dietitian in the care of these patients is of essence. Attention needs to be given not only to the supplementation of macronutrients and calories, but also micronutrients and vitamins (especially the fat-soluble vitamins A, D, E and K). As will be discussed below, one of the indications of preoperative biliary drainage is nutritional optimisation in malnourished individuals. This is based on the common understanding that pancreatic resectional surgery remains a procedure with attendant morbidity and even the risk of mortality [32]. Enteral nutrition is the favoured route. If the patient is unable to tolerate, or be able to fulfil nutritional requirement goals, using the oral route, then consideration of placement of a nasojejunal/nasogastric tube for feeding needs to be considered. It is less likely that a

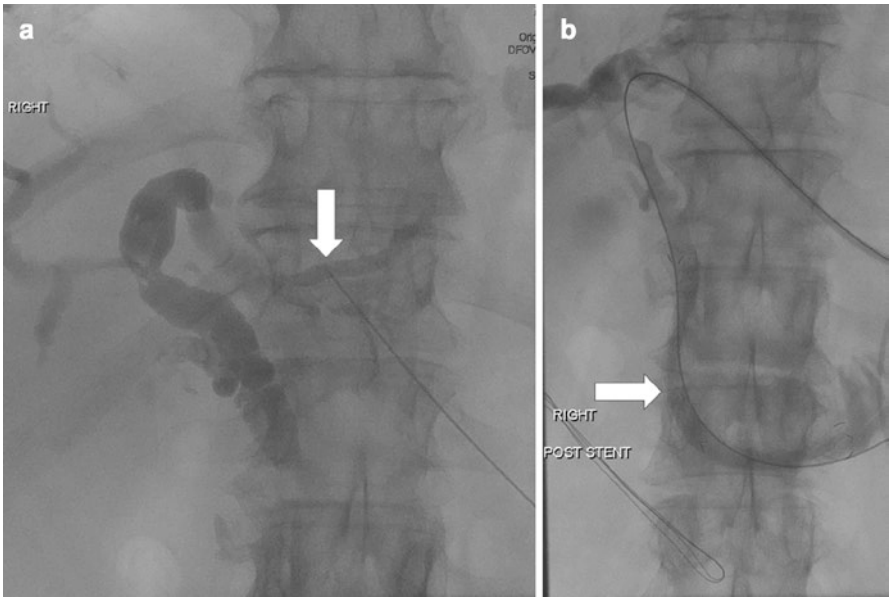

Fig. 41.2 Image intensifier screening demonstrating Percutaneous biliary drainage for a lower bile duct obstruction resulting in upstream intra- and extra-hepatic biliary drainage. (**a**) Left hepatic duct puncture/access marked by the white arrow; (**b**) biliary stent across the stricture marked by a white arrow. (*Acknowledgement: Dr Adam Koukourou, Head of Interventional Radiology, Flinders Medical Centre, Australia, for providing this image*)

patient with resectable pancreatic cancer and obstructive jaundice will need total parenteral nutrition. In such patients, it important to look for metastases in order to avoid an operation that is morbid and would be unlikely to result in a meaningful survival.

Correction of coagulopathy secondary to obstructive jaundice is important prior to any intervention (Box 41.2).

41.5 Techniques of Preoperative Biliary Drainage (Table 41.1 [33, 34])

The two access routes for preoperative biliary drainage in pancreatic head cancer are per os endoscopic and percutaneous transhepatic. Endoscopic biliary drainage, by ERCP, can be by plastic internal stent, nasobiliary external drain and self-expanding metal stent (SEMS: covered, partially covered or uncovered) (Figs. 41.3, 41.4, and 41.5). Percutaneous drainage, by ultrasound guided interventional radiology, can be external drainage (with catheter above the obstruction or through the obstruction into the duodenum) and internal drainage (with plastic or SEMS stent). Endoscopic ultrasound (EUS)-guided biliary drainage has recently reported,

Box 41.2 Management of Coagulopathy in a Patient with Obstructive Jaundice

Determine the cause of coagulopathy

- Obstruction of common bile duct by cancer
- Other contributing causes (e.g. liver disease/cirrhosis)
- Use of anticoagulants (indication, drug, dose)

Specific blood investigations

- Complete blood count, including platelet count
- Prothrombin time and international normalised ratio (INR)
- Activated partial thromboplastin time (APTT)
- Extended coagulation profile (e.g. rotational thromboelastometry, ROTEM)

Treatment of coagulopathy

- Treat expected coagulopathy prior to any intervention
  - Vitamin K (10 mg intravenously, and repeat if required)
  - Fresh Frozen plasma (15 ml/kg body weight) if Vitamin K resistant
- If INR >1.5 consider biliary drainage (see above)
- If coagulopathy due to underlying liver disease, refer to Hepatology
- If coagulopathy due to anticoagulants, refer to Haematology

Table 41.1 Techniques of preoperative biliary drainage with their advantages and disadvantages

Technique	Advantage	Disadvantage
Endoscopic[a]		
Metal (SEMS) stent	Longer drainage time Lower rate of reintervention Lower preoperative cholangitis	Higher preoperative pancreatitis Higher wound infection rates[b] Higher post-operative complication rates[b]
Plastic stent	Lower preoperative pancreatitis	Lower drainage time Higher rate of reintervention Higher preoperative cholangitis Higher wound infection rates[b] Higher post-operative complication rates[b]
Percutaneous		
PTBD	Lower risk of post-operative haemorrhage[b]	Higher wound infection rates[b] Higher post-operative complication rates[b]

SEMS self-expanding metal stent, *PTBD* percutaneous transhepatic biliary drainage
[a]Advantages are based on comparison between plastic and metal
[b]Compared to no drainage

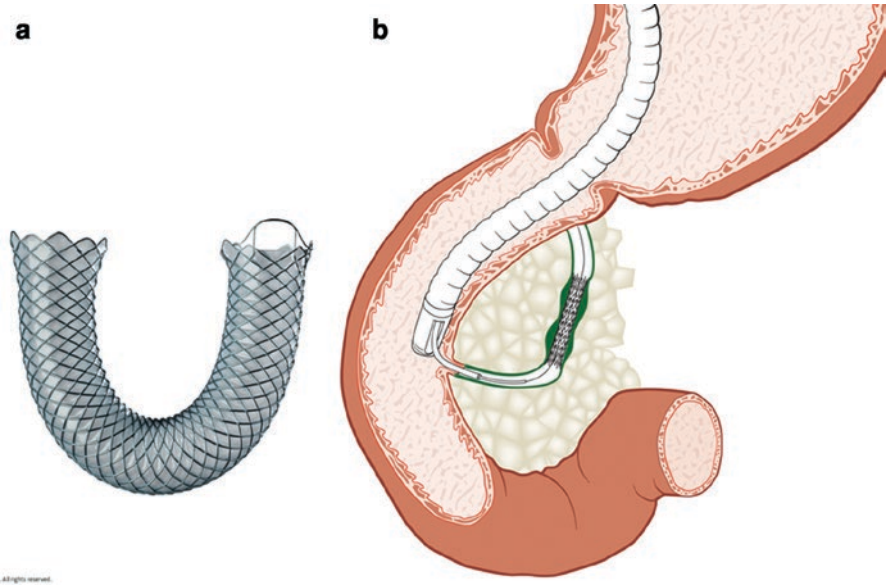

Fig. 41.3 (**a**) Covered self-expanding metallic stent/SEMS (*reproduced with permission from Boston Scientific, Australia*); (**b**) Diagrammatic representation of endoscopic retrograde cholangiopancreatography (ERCP) with placement of a SEMS. (*Artwork by Eric Lum, Medical Artist, Flinders Medical Centre, Adelaide—South Australia*)

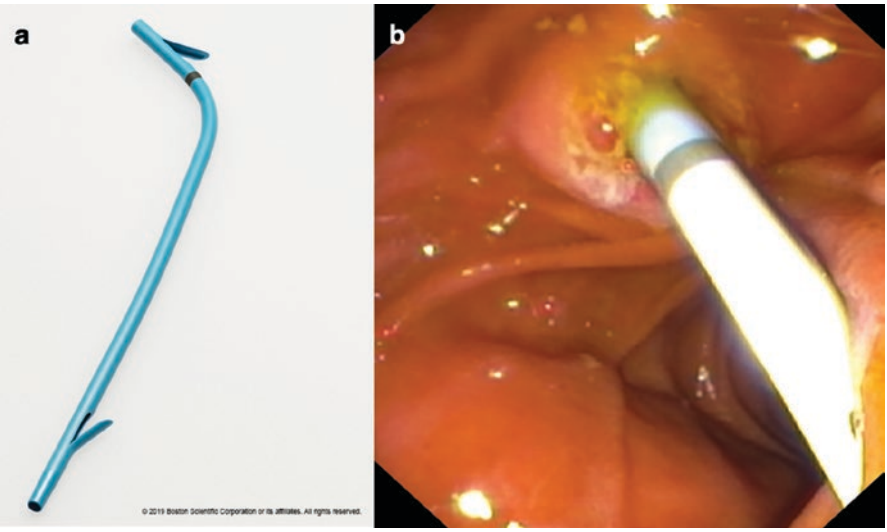

Fig. 41.4 (**a**) Plastic biliary stent (*reproduced with permission from Boston Scientific, Australia*); (**b**) Side-viewing endoscopic image of a successfully deployed plastic stent across an obstructing lower common bile duct stricture

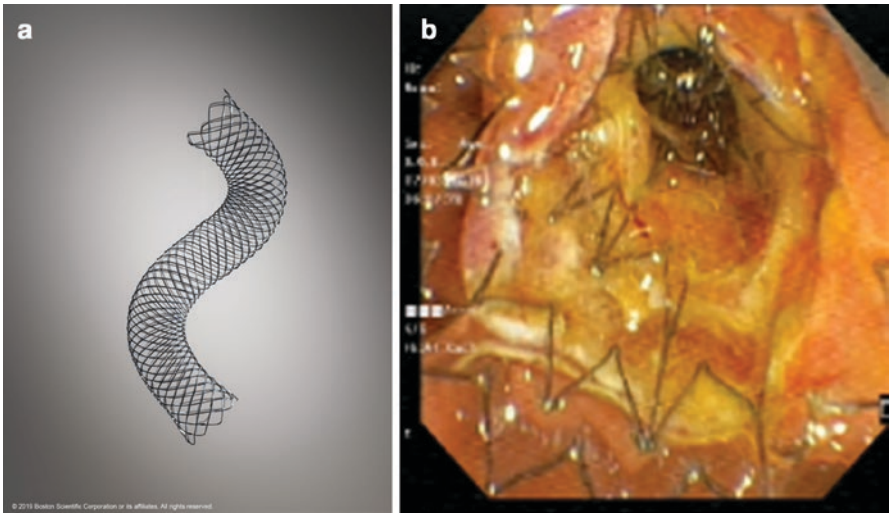

Fig. 41.5 (**a**) Uncovered self-expanding metallic stent/SEMS (*reproduced with permission from Boston Scientific, Australia*); (**b**) Side-viewing endoscopic image of a successfully deployed SEMS across an obstructing lower common bile duct stricture. (*Reproduced with permission from book chapter: Barreto SG. Pancreatic Cancer. In: Surgical Diseases of the Pancreas and Biliary Tree. Editors. Barreto SG, Windsor JA. Springer Nature 2018*)

including tube cholecystoduodenostomy and tube choledochoduodenostomy [35]. However, these procedures remain experimental and would appear to be more appropriate for palliation of obstructive jaundice in patients with unresectable pancreatic head cancer. It is unlikely that these procedures will replace endoscopic or percutaneous biliary drainage in this setting.

A recent network meta-analysis [33] compared endoscopic (plastic vs. metal stents) and percutaneous drainage, and found that there was insufficient evidence to determine the best type of preoperative biliary drainage. There is some evidence to support the use of endoscopic SEMS over plastic stents [36]. The randomized controlled trial by Tol et al. [37] found that endoscopic plastic stents were associated with higher procedure-related complications (46% vs. 24%, $p < 0.011$), stent-related occlusion/exchange rates (30% vs. 6%; $P < 0.003$) and surgical complications (74% vs. 51%; $P < 0.006$), when compared to endoscopic SEMS.

There appears to be no differences between covered and uncovered SEMS in terms of efficacy and complication rates. Uncovered or partially covered stents, by permitting tumour and tissue ingrowth, are less likely to migrate in comparison to fully covered stents [38, 39]. Thus, while the former may be preferred in palliative scenarios [40], the latter would be better suited to situations where removal of the stent maybe indicated as in the pre-operative following neoadjuvant therapy. From a cost perspective, there appears to be no difference between plastic stents and SEMS (fully covered and uncovered). Fully covered stents tend to result in fewer delays in neoadjuvant treatment because of the lower rates of stent occlusion. This offers another reason for their preference in patients requiring preoperative biliary

drainage, especially if they are to receive neoadjuvant therapy [41]. The addition of an anti-migration system to the fully covered SEMS may remove the small risk of stent migration [42].

A situation where a SEMS is inadvisable is in the context of irreversible electroporation (IRE). This may occur when surgical exploration reveals unexpected unresectable locally advanced disease that is amenable to irreversible electroporation (IRE), where SEMS is a contraindication [43]. In this situation the SEMS will need to be removed prior IRE [44].

41.6 Obstructive Jaundice in Pancreatic Head Cancer: To Drain or Not to Drain!

Despite the complications (above) there is a role for preoperative biliary drainage in patients with resectable and borderline resectable pancreatic head cancer patients.

41.6.1 Indications for Preoperative Biliary Drainage

Figure 41.6 presents a treatment algorithm for the management of pancreatic head cancer patients with obstructive jaundice. The main indications for considering preoperative biliary drainage are the following:

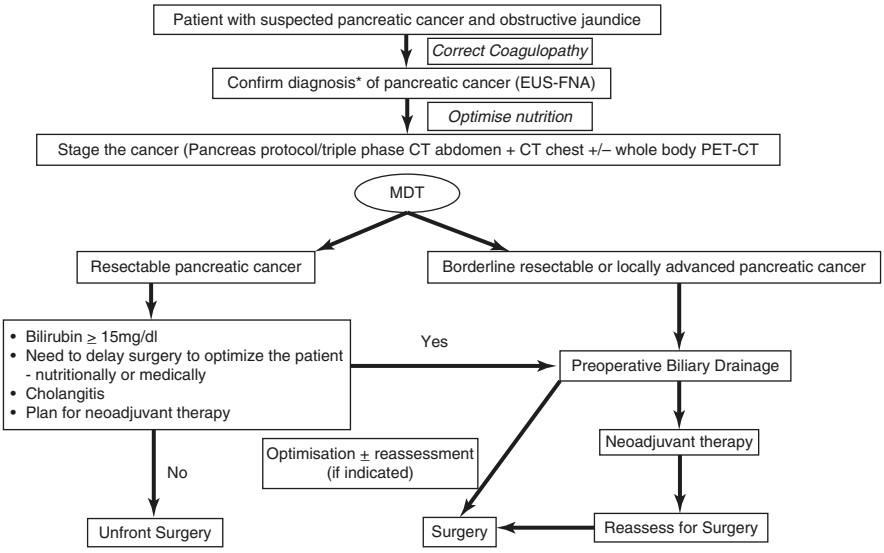

Fig. 41.6 Treatment algorithm outlining the approach to the management of pancreatic cancer patients with obstructive jaundice

41.6.1.1 Cholangitis

Cholangitis secondary to any obstructing pathology, including cancer, is a medical emergency that warrants biliary drainage [45]. Cholangitis is clinically manifested in 50–75% of patients by the symptom complex including fever, right abdominal pain and jaundice referred to as *Charcot's triad*. Patients who are in severe sepsis, as a result of cholangitis, may also manifest lethargy and mental confusion (Reynold's pentad). The risk of pancreatic head resection increases in the presence of cholangitis (reference). Note that cholangitis can occur without prior bile duct instrumentation. Bactibilia has been found in patients undergoing upfront surgery (see above) indicating that the biliary tree is not a sterile, closed system. Protective mechanism prevent colonization and cholangitis, and include continuous flushing of bile flow, secretions of the biliary epithelium (including mucus), bacteriostatic effects of bile salts and secretory immunoglobulin A (sIgA) [46]. Biliary drainage once again restores the bilio-enteric continuity and free drainage of bile, thereby ameliorating cholangitis allowing the patient time to recover to have a safe operation.

41.6.1.2 Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is indicated in patients with borderline resectable [47, 48] and is now being extended to patients with locally advanced pancreatic head cancer [49] and resectable pancreatic head cancer [50]. The safe administration of chemotherapy requires near normal liver function and a bilirubin level <1.5 times the upper limit of normal [50]. Thus, in patients with obstructive jaundice, preoperative biliary drainage may be necessary to improve liver function in patients being referred for neoadjuvant chemotherapy.

41.6.1.3 Delays in Surgery

The potential reasons for delayed surgery are many, but include:

- *Logistical*: The concept of regionalization of care is supported by the finding of improved outcomes for pancreatic head cancer surgery [51] in centres with high procedural volumes [52]. Referral to a regional centre may delay surgery [53].
- *Patient-related*: Significant co-morbidities may delay surgery because of the need for the treatment of reversible organ dysfunction, and preoperative biliary drainage will be necessary in some patients.

41.6.1.4 Elevated Bilirubin

The cut-off level of bilirubin for preoperative biliary drainage, in the absence of cholangitis, has varied. The published cut-off values vary from 7.5 mg/dL (or 128 μmol/L) to 15 mg/dL (256 μmol/L) [54, 55]. This wide range reflects

differences in philosophy and comfort level with individual surgeon. There are risks associated with preoperative biliary drainage must be weighed against the risks of no drainage (including cholangitis and coagulopathy). Serum bilirubin levels ≥15 mg/dL, which is associated with increased morbidity and mortality [56], is a widely accepted as an indication for preoperative biliary drainage.

41.7 Optimal Timing of Surgery Post-biliary Drainage

While there is no evidence for an ideal time from the time of preoperative biliary drainage to surgery for pancreatic head cancer, the preference is for a delay of 4–6 weeks [32, 57]. The rationale for this approach is based on the premise that a delay of less than 4 weeks is insufficient for recovery of hepatic function following drainage, and a delay of more than 6 weeks increases the risk of bactibilia and stent-related complications [58].

41.8 Complications of Preoperative Biliary Drainage

There have been numerous reports of stent related complications and failures, including the need for preoperative stent exchanges, cholangitis, and perioperative morbidity (wound infections [59] and haemorrhage). Stent-related complications are higher for plastic stents (38–93%) than for metal stents (0–15%) [33]. The DROP (DRainge vs. OPeration) trial [60] which randomised patients to either up front surgery or preoperative biliary drainage with a plastic stent noted a significantly higher serious complication rate in the preoperative biliary drainage group (39% vs. 74% $p < 0.001$) secondary to complications that occurred before surgery and not necessarily due to a difference in post-operative complications.

41.8.1 Effect on Perioperative Morbidity and Mortality

A recent meta-analysis of the literature comparing preoperative biliary drainage with upfront surgery concluded that preoperative biliary drainage results in an increase in overall complications (Odds ratio, OR: 1.40) and in wound infections (OR: 1.94). There was not increase in mortality rate, incidence of pancreatic fistula, or intra-abdominal abscess formation. The effect of preoperative biliary drainage on post-pancreatectomy haemorrhage (PPH) remains unclear as two large studies (≥1000 patients each) had contradictory results, with one study indicated that preoperative biliary drainage was a risk factor for PPH [61], the other found no such influence [54]. A recent network meta-analysis suggests that preoperative biliary

drainage, especially by the percutaneous route, was associated with a lower risk of PPH when compared with upfront surgery [33].

41.8.2 Effect on Bactibilia

Preoperative biliary drainage is accompanied by bactibilia [62] which appears to be associated with an increased risk wound infections [63]. It has been found that bactibilia is present in 64% of patients following preoperative biliary drainage compared with 18% of patients who had upfront surgery [64].

41.8.3 Effect on Overall Survival

The negative effects of obstructive jaundice on overall survival in pancreatic head cancer may, in part, be explained on the fact that a cicatrizing tumour that occludes the distal bile duct is more likely to be an inherently aggressive cancer [2]. Preoperative biliary drainage and its associated delay in surgery appears to not increase or decrease overall survival [65].

41.8.4 Complications Specific to ERCP and Stenting

41.8.4.1 Stent-Related Problems

Another problem with preoperative biliary drainage is the risk of stent occlusion necessitating stent exchanges. A systematic review and meta-analysis of the literature comparing plastic versus SEMS has shown that SEMS are associated with a significantly lower rate of re-intervention (OR: 0.30; $p < 0.008$) [34].

The use of endoscopic stents for preoperative biliary drainage has been said to increase the difficulty of surgery because of the inflammatory response. Olsson et al. [66], in their randomized controlled trial used various surrogate markers (including an objective reporting by the surgeon about the difficulty of the hepatoduodenal dissection and the ease of extracting the stent and performance of the hepaticojejunostomy) to compare SEMS versus plastic stents. They found no difference.

41.8.4.2 Cholangitis

One of the indications for preoperative biliary drainage is cholangitis. However, it must be appreciated that cholangitis is also an important complication of the procedure, usually secondary to blockage of the endoscopically placed stent [60]. This is

diagnosed by a combination of a clinical signs and ultrasound imaging indicating an absence of pneumobilia.

41.8.4.3 Pancreatitis

Another complication of ERCP and stent placement is pancreatitis. This has been reported in 7% of patients [60] and occurs either due to the raised intraductal pressure from injection of contrast at the time of the procedure, or the stent occluding the pancreatic duct. Pancreatitis is more likely to occur with SEMS than with plastic stents (OR = 3.60, 95% CI = 1.62–7.98, P = 0.002) [34]. It is more common in covered SEMS as compared to uncovered ones [67].

41.8.5 Complications Specific to PTBD

Complications specific to PTBD include bleeding (arterial or venous) noted in 2–5% of patients and is more common in left sided drainage [68]. Other complications include bile leak into the peritoneum or through to the skin with resultant skin irritation and break down [69]. Pain is another important symptom. It may arise from the catheter, itself, or from cholecystitis or pancreatitis. The latter may arise from the catheter running across the origin of the pancreatic and cystic ducts. Less frequently (2% of patients) transient bacteremia and sepsis have been reported [70].

41.9 The Role of Antibiotics with Preoperative Biliary Drainage?

Prophylactic antibiotics are recommended before drainage because of the risk of transient bacteremia and sepsis. There is no need for ongoing antibiotics following biliary drainage unless the patient has cholangitis or a definite source of sepsis. Prophylactic antibiotics are also indicated prior to resection of pancreatic head cancer, irrespective of whether preoperative biliary drainage was performed or not [59, 62, 64, 71]. Ertapenem, administered as a once daily perioperative 3-day course has been shown to reduce the risk of infectious- and overall-complications [64]. The choice of prophylactic antibiotics, before drainage and before surgery, will be guided by local hospital protocols.

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References

1. Schmidt-Hansen M, Berendse S, Hamilton W. Symptoms of pancreatic cancer in primary care: a systematic review. Pancreas. 2016;45(6):814–8.
2. Strasberg SM, Gao F, Sanford D, Linehan DC, Hawkins WG, Fields R, et al. Jaundice: an important, poorly recognized risk factor for diminished survival in patients with adenocarcinoma of the head of the pancreas. HPB (Oxford). 2014;16(2):150–6.
3. Monastyrski N, Tilling G. Zur Frage von der chirurgischen Behandlung der vollständigen Undurchgängigkeit des Ductus choledochus. Zentralbl Chir. 1888;15:778–9.
4. Murphy J. Cholecysto-intestinal, gastro-intestinal, entero-intestinal anastomosis, and approximation without sutures. Med Rec (NY). 1892;42:665–76.
5. Shukla P, Barreto S, Shrikhande S. The evolution of pancreatoduodenectomy. Hepato-Gastroenterology. 2011;58(109):1409–12.
6. Hirschel G. Die Resektion des Duodenums mit der Papille wegen Karzinoms. Munchen Med Wochenschr. 1914;61:1728–9.
7. Kausch W. Das carcinom der papilla duodeni und seine radikale entfernung. Beitr Klin Chir. 1912;78:471–624.
8. Halsted W. Contribution to the surgery of the bile passages, especially of the common bile-duct. Boston Med Surg J. 1899;41:645–54.
9. Whipple A, Parsons W, Mullins C. Treatment of carcinoma of the ampulla of Vater. Ann Surg. 1935;102:763–79.
10. Nakayama T, Ikeda A, Okuda K. Percutaneous transhepatic drainage of the biliary tract: technique and results in 104 cases. Gastroenterology. 1978;74(3):554–9.
11. Denning DA, Ellison EC, Carey LC. Preoperative percutaneous transhepatic biliary decompression lowers operative morbidity in patients with obstructive jaundice. Am J Surg. 1981;141(1):61–5.
12. Glenn F, Evans JA, Mujahed Z, Thorbjarnarson B. Percutaneous transhepatic cholangiography. Ann Surg. 1962;156:451–62.
13. Hatfield AR, Tobias R, Terblanche J, Girdwood AH, Fataar S, Harries-Jones R, et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet. 1982;2(8304):896–9.
14. McPherson GA, Benjamin IS, Hodgson HJ, Bowley NB, Allison DJ, Blumgart LH. Preoperative percutaneous transhepatic biliary drainage: the results of a controlled trial. Br J Surg. 1984;71(5):371–5.
15. Pitt HA, Gomes AS, Lois JF, Mann LL, Deutsch LS, Longmire WP Jr. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg. 1985;201(5):545–53.
16. Lygidakis NJ, van der Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. Acta Chir Scand. 1987;153(11-12):665–8.
17. Marcus SG, Dobryansky M, Shamamian P, Cohen H, Gouge TH, Pachter HL, et al. Endoscopic biliary drainage before pancreaticoduodenectomy for periampullary malignancies. J Clin Gastroenterol. 1998;26(2):125–9.
18. Sugiyama H, Tsuyuguchi T, Sakai Y, Nisikawa T, Miyazaki M, Yokosuka O. Preoperative drainage for distal biliary obstruction: endoscopic stenting or nasobiliary drainage? Hepato-Gastroenterology. 2013;60(122):231–4.
19. Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet. 1987;2(8550):57–62.
20. Sewnath ME, Birjmohun RS, Rauws EA, Huibregtse K, Obertop H, Gouma DJ. The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg. 2001;192(6):726–34.

21. Scheufele F, Schorn S, Demir IE, Sargut M, Tieftrunk E, Calavrezos L, et al. Preoperative biliary stenting versus operation first in jaundiced patients due to malignant lesions in the pancreatic head: a meta-analysis of current literature. Surgery. 2017;161(4):939–50.
22. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg. 1999;230(2):131–42.
23. Vogel A, Kullmann F, Kunzmann V, Al-Batran SE, Oettle H, Plentz R, et al. Patients with advanced pancreatic cancer and hyperbilirubinaemia: review and German expert opinion on treatment with nab-paclitaxel plus gemcitabine. Oncol Res Treat. 2015;38(11):596–603.
24. Kremer AE, Martens JJ, Kulik W, Rueff F, Kuiper EM, van Buuren HR, et al. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. Gastroenterology. 2010;139(3):1008–18, 18.e1.
25. Bassari R, Koea JB. Jaundice associated pruritis: a review of pathophysiology and treatment. World J Gastroenterol. 2015;21(5):1404–13.
26. Armstrong CP, Dixon JM, Duffy SW, Elton RA, Davies GC. Wound healing in obstructive jaundice. Br J Surg. 1984;71(4):267–70.
27. Pavlidis ET, Pavlidis TE. Pathophysiological consequences of obstructive jaundice and perioperative management. Hepatobil Pancreat Dis Int. 2018;17(1):17–21.
28. Rodarte-Shade M, Kahaleh M. Stent placement as a bridge to surgery in malignant biliary obstruction (pancreatic cancer, distal bile duct cancer, and hilar tumors). Gastrointest Interv. 2015;4:21–6.
29. Myatra S, Divatia JV, Jibhkate B, Barreto GS, Shrikhande SV. Preoperative assessment and optimization in periampullary and pancreatic cancer. Indian J Cancer. 2011;48(1):86–93.
30. Wang L, Yu WF. Obstructive jaundice and perioperative management. Acta Anaesthesiol Taiwanica. 2014;52(1):22–9.
31. Barreto SG. Pancreatic cancer: let us focus on cachexia, not just sarcopenia! Future Oncol. 2018;14(27):2791–4.
32. Barreto SG, Singh A, Perwaiz A, Singh T, Adlakha R, Singh MK, et al. The cost of pancreatoduodenectomy - an analysis of clinical determinants. Pancreatology. 2016;16:652.
33. Lee PJ, Podugu A, Wu D, Lee AC, Stevens T, Windsor JA. Preoperative biliary drainage in resectable pancreatic cancer: a systematic review and network meta-analysis. HPB (Oxford). 2018;20(6):477–86.
34. Liu P, Lin H, Chen Y, Wu YS, Tang M, Liu C. Comparison of metal and plastic stents for preoperative biliary drainage in resectable and borderline resectable periampullary cancer: a meta-analysis and system review. J Laparoendosc Adv Surg Tech A. 2018;28(9):1074–82.
35. Iwashita T, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. Clin J Gastroenterol. 2014;7(2):94–102.
36. Crippa S, Cirocchi R, Partelli S, Petrone MC, Muffatti F, Renzi C, et al. Systematic review and meta-analysis of metal versus plastic stents for preoperative biliary drainage in resectable periampullary or pancreatic head tumors. Eur J Surg Oncol. 2016;42(9):1278–85.
37. Tol JA, van Hooft JE, Timmer R, Kubben FJ, van der Harst E, de Hingh IH, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2016;65(12):1981–7.
38. Seo DW, Sherman S, Dua KS, Slivka A, Roy A, Costamagna G, et al. Covered and uncovered biliary metal stents provide similar relief of biliary obstruction during neoadjuvant therapy in pancreatic cancer: a randomized trial. Gastrointest Endosc. 2019;90:602.
39. Yokota Y, Fukasawa M, Takano S, Kadokura M, Shindo H, Takahashi E, et al. Partially covered metal stents have longer patency than uncovered and fully covered metal stents in the management of distal malignant biliary obstruction: a retrospective study. BMC Gastroenterol. 2017;17(1):105.
40. Conio M, Mangiavillano B, Caruso A, Filiberti RA, Baron TH, De Luca L, et al. Covered versus uncovered self-expandable metal stent for palliation of primary malignant extrahepatic biliary strictures: a randomized multicenter study. Gastrointest Endosc. 2018;88(2):283–91.e3.

41. Gardner TB, Spangler CC, Byanova KL, Ripple GH, Rockacy MJ, Levenick JM, et al. Cost-effectiveness and clinical efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial. Gastrointest Endosc. 2016;84(3):460–6.
42. Kitano M, Yamashita Y, Tanaka K, Konishi H, Yazumi S, Nakai Y, et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. Am J Gastroenterol. 2013;108(11):1713–22.
43. Angiodynamics [Internet]. 2010: the first surgical ablation system based on Irreversible Electroporation Technology. Available from: http://www.erickortzmd.com/wp-content/uploads/2011/04/NanoKnife.pdf.
44. Mansson C, Nilsson A, Karlson BM. Severe complications with irreversible electroporation of the pancreas in the presence of a metallic stent: a warning of a procedure that never should be performed. Acta Radiol Short Rep. 2014;3(11):2047981614556409.
45. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, et al. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. Br J Surg. 2013;100(12):1589–96.
46. Sung JY, Costerton JW, Shaffer EA. Defense system in the biliary tract against bacterial infection. Dig Dis Sci. 1992;37(5):689–96.
47. Barreto S, Windsor J. Justifying vein resection with pancreatoduodenectomy. Lancet Oncol. 2016;17(3):e118–e24.
48. Windsor JA, Barreto SG. The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future? J Gastrointest Oncol. 2017;8(1):189–93.
49. Napolitano F, Formisano L, Giardino A, Girelli R, Servetto A, Santaniello A, et al. Neoadjuvant treatment in locally advanced pancreatic cancer (LAPC) patients with FOLFIRINOX or gemcitabine nabpaclitaxel: a single-center experience and a literature review. Cancers (Basel). 2019;11(7):981.
50. van Veldhuisen E, van den Oord C, Brada LJ, Walma MS, Vogel JA, Wilmink JW, et al. Locally advanced pancreatic cancer: work-up, staging, and local intervention strategies. Cancers (Basel). 2019;11(7):976.
51. Shukla PJ, Barreto SG, Bedi M, Bheerappa N, Chaudhary A, Gandhi M, et al. Peri-operative outcomes for pancreatoduodenectomy in India: a multi-centric study. HPB (Oxford). 2009;11(8):638–44.
52. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. CA Cancer J Clin. 2009;59(3):192–211.
53. Marchegiani G, Andrianello S, Perri G, Secchettin E, Maggino L, Malleo G, et al. Does the surgical waiting list affect pathological and survival outcome in resectable pancreatic ductal adenocarcinoma? HPB (Oxford). 2018;20(5):411–7.
54. De Pastena M, Marchegiani G, Paiella S, Malleo G, Ciprani D, Gasparini C, et al. Impact of preoperative biliary drainage on postoperative outcome after pancreaticoduodenectomy: an analysis of 1500 consecutive cases. Dig Endosc. 2018;30(6):777–84.
55. Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: enhanced recovery after surgery (ERAS(R)) Society recommendations. World J Surg. 2013;37(2):240–58.
56. Bolm L, Petrova E, Woehrmann L, Werner J, Uhl W. The impact of preoperative biliary stenting in pancreatic cancer: a case-matched study from the German nationwide pancreatic surgery registry (DGAV StuDoQ| Pancreas). Pancreatology. 2019;19:985.
57. Shrikhande SV, Barreto SG, Somashekar BA, Suradkar K, Shetty GS, Talole S, et al. Evolution of pancreatoduodenectomy in a tertiary cancer center in India: improved results from service reconfiguration. Pancreatology. 2013;13(1):63–71.
58. Sandini M, Honselmann KC, Birnbaum DJ, Gavazzi F, Chirica M, Wellner U, et al. Preoperative biliary stenting and major morbidity after pancreatoduodenectomy: does elapsed time matter?: the FRAGERITA study group. Ann Surg. 2018;268(5):808–14.

59. Barreto SG, Singh MK, Sharma S, Chaudhary A. Determinants of surgical site infections following pancreatoduodenectomy. World J Surg. 2015;39(10):2557–63.
60. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129–37.
61. Wellner UF, Kulemann B, Lapshyn H, Hoeppner J, Sick O, Makowiec F, et al. Postpancreatectomy hemorrhage--incidence, treatment, and risk factors in over 1,000 pancreatic resections. J Gastrointest Surg. 2014;18(3):464–75.
62. Sourrouille I, Gaujoux S, Lacave G, Bert F, Dokmak S, Belghiti J, et al. Five days of postoperative antimicrobial therapy decreases infectious complications following pancreaticoduodenectomy in patients at risk for bile contamination. HPB (Oxford). 2013;15(6):473–80.
63. Howard TJ, Yu J, Greene RB, George V, Wairiuko GM, Moore SA, et al. Influence of bactibilia after preoperative biliary stenting on postoperative infectious complications. J Gastrointest Surg. 2006;10(4):523–31.
64. Barreto S, Singh A, Perwaiz A, Singh T, Singh M, Sharma S, et al. Perioperative antimicrobial therapy in preventing infectious complications following pancreatoduodenectomy. Indian J Med Res. 2017;146:514.
65. Eshuis WJ, van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, Kuipers EJ, et al. Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. Ann Surg. 2010;252(5):840–9.
66. Olsson G, Frozanpor F, Lundell L, Enochsson L, Ansorge C, Del Chiaro M, et al. Preoperative biliary drainage by plastic or self-expandable metal stents in patients with periampullary tumors: results of a randomized clinical study. Endosc Int Open. 2017;5(9):E798–808.
67. Lee SJ, Kim MD, Lee MS, Kim IJ, Park SI, Won JY, et al. Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial. J Vasc Interv Radiol. 2014;25(12):1912–20.
68. Yarmohammadi H, Covey AM. Percutaneous biliary interventions and complications in malignant bile duct obstruction. Chin Clin Oncol. 2016;5(5):68.
69. Robson PC, Heffernan N, Gonen M, Thornton R, Brody LA, Holmes R, et al. Prospective study of outcomes after percutaneous biliary drainage for malignant biliary obstruction. Ann Surg Oncol. 2010;17(9):2303–11.
70. Winick AB, Waybill PN, Venbrux AC. Complications of percutaneous transhepatic biliary interventions. Tech Vasc Interv Radiol. 2001;4(3):200–6.
71. Nagino M, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Kondo S, et al. Preoperative biliary drainage for biliary tract and ampullary carcinomas. J Hepato-Biliary-Pancreat Surg. 2008;15(1):25–30.

Chapter 42
Nutritional Support and Therapy Before and After Pancreatic Surgery

Luca Gianotti, Marta Sandini, and Thilo Hackert

Take Home Messages

- The preoperative assessment of the nutritional status and risk should be part of the routine practice
- Consultation and follow-up with a nutritionist/dietitian are encouraged during the neoadjuvant therapy
- The implementation of enhanced recovery after surgery programs facilitates postoperative functional and nutritional recovery
- The technique of intestinal reconstruction after pancreatoduodenectomy does not significantly affect the rate of delayed gastric emptying and long-term nutritional status
- Appropriate timing of the nutritional support and therapy can positively affect short- and long-term outcomes
- If postoperative artificial nutrition is needed, enteral feeding is the best choice
- There is no evidence to show the benefit of avoiding oral intake in patients who are complicated by a clinically relevant postoperative pancreatic fistula after surgery, and there are no criteria for who can and who should not be fed orally. Stable patients with a grade B-postoperative pancreatic fistula may well tolerate oral diets, while grade C-postoperative pancreatic fistula severely affects the patient capability to be fed orally

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Pearls and Pitfalls

Pearls:

- There is sufficient evidence to suggest the utmost role of an adequate nutritional support and therapy in affecting short- and long-term outcomes after major pancreatic resections.

Pitfalls:

- Surgeon awareness on the importance of this therapy and the correct integration of appropriate nutritional support into the overall management of patients undergoing pancreatic resection need to be implemented.

Further Perspective

- The effects of neoadjuvant treatments on nutritional status and body composition need further investigation.
- Which subset of patients may benefit most of nutritional support during the delivery of the neoadjuvant chemoradiation is unclear.
- Whether nutritional supplementation needs to be implemented routinely after pancreatoduodenectomy has to be assessed.
- Further research on the optimal dose of pancreatic enzyme replacement therapy and which subset of patients may benefit most is warrant.
- Non-alcoholic fatty liver disease is a poorly recognized and investigated complication of exocrine pancreatic insufficiency particularly in long-term survivors.

42.1 Introduction

Major surgery produces intense changes in metabolism and nutritional status through the activation of an inflammatory cascade and the release of stress hormones; this response appears to be proportional to the extent of the operative trauma. Pancreatic resections are recognized as one of the most challenging operations because of the magnitude of the dissection and resection, the resultant global stress, and the relatively high rate of morbidity. Appropriate tissue healing and recovery/maintenance of organ function after such operations can lead to an effective and efficient metabolic response, which in turn necessitates adequate qualitative and quantitative nutritional substrates to be effective. Moreover, obstructive jaundice, when present, is invariably associated with impairment of absorption, nutritional state and homeostasis [1].

Martin et al. [2], in a recent international survey, reported that the management of perioperative nutrition in patients undergoing pancreatoduodenectomy is very disparate.

The aim of this chapter is to provide evidence to support the key role of the nutritional therapy in pancreatic surgery.

42.2 Preoperative Evaluation of the Nutritional Status, Malnutrition Risk and Anthropometry

The rate of patients with pancreatic ductal adenocarcinoma (PDAC) who experience body weight loss (WL) or have moderate to high risk of malnutrition at diagnosis is greater than 50% [3].

The development and progression of malnutrition can be related to decreased food intake and increased catabolism [4]. Several nutritional assessment scores have been developed to determine the magnitude of malnutrition and the risk of developing it [5]. All these metrics are based primarily on subjective questionnaires and they are easy to calculate and practical to use at the time of diagnosis. However, the percentage of patients at high risk for malnutrition varies between the scores, and the patients assigned as high risk by these scores were not significantly prone to more postoperative complications [6]. Because these high-risk patients should be candidates for perioperative nutritional support, the discrepancy in predicting poor outcomes with different nutritional screening tools might lead to either nutritional under- or over-treatment with potential detrimental effects.

Body composition, in particular the measurement of muscle mass and visceral fat, cannot be determined accurately by measuring BMI, because the proportions of these body compartments may be abnormal in malnourished as well as in normal weight or even in obese patients [7].

Recent data showed a strong association between preoperative muscle wasting and worse postoperative outcomes. Depletion of skeletal muscle was also an independent predictor of clinically relevant postoperative pancreatic fistula (POPF), increased duration of in-hospital stay, and discharge to a non-home facility. The combination of excessive intraabdominal adipose tissue and loss of muscle mass, a syndrome called “sarcopenic obesity”, has been also shown to be a major determinant of procedure-related morbidity and mortality [8, 9].

When considering long-term outcomes, sarcopenic patients had a decreased overall survival when compared with non-sarcopenic patients [10–12], and, for pancreatic cancer patients, sarcopenia was associated with poor tolerance to adjuvant chemotherapy [13] and an earlier recurrence of disease [14].

New data suggest that locally advanced pancreatic cancer can be treated successfully with neoadjuvant chemo- or chemoradiation to downstage the disease [15]. The effects of neoadjuvant treatments on nutritional status and body composition have been poorly investigated. Guidelines support the use of nutritional interventions during the delivery of the neoadjuvant chemoradiation in selected cases [16].

Adverse effects of chemo-radiation, including anorexia, nausea and vomiting, and diarrhea may lead to a rapid worsening of the nutritional status and depletion of lean body mass [17, 18]. One study [19] highlighted the adverse effects of neoadjuvant treatments on nutritional status, but also reported the encouraging increase in serum albumin levels after completion of the neoadjuvant chemotherapy and before operative exploration. Dalal et al. [20], showed that neoadjuvant chemotherapy caused weight loss, but the body compartment affected the most was the fatty compartment, with preservation or even in some patients, a gain in skeletal muscle mass.

A study including patients with borderline or locally advanced PDAC who received neoadjuvant chemotherapy showed a significant loss of adipose tissue, but there was minimal or no wasting of lean body mass during treatment. Moreover, an increase in muscle mass during treatment was a strong predictor of resectability [21].

Indeed, consultation and follow-up with a nutritionist/dietitian are strongly encouraged during the neoadjuvant therapy.

42.3 Indications to Pre-operative Nutritional Support

The guidelines of European and American societies [22, 23] developed for major abdominal operations may be accepted also for pancreatic surgery in this specific cohort.

The benefit of preoperative nutritional support was only documented in patients with severe malnutrition - or with high risk of developing malnutrition - who were fed parenterally or enterally for at least 7 days prior to surgery. The definition of severe malnutrition has now been updated by the GLIM criteria [24] (Table 42.1)

Table 42.1 The Global Leadership Initiative on Malnutrition (GLIM) thresholds for severity grading of malnutrition based of phenotypic criteria [24]

	Weight loss (%)	Body mass index	Reduced muscle mass[a]
Moderate malnutrition	5–10% with past 6 mo. or 10–20% beyond 6 months	<20 if <70 years <22 if ≥70 years	Mild to moderate
Severe malnutrition	> 10% with past 6 months or >20% beyond 6 months	<18.5 if <70 years <20 if ≥70 years	Severe

Functional assessments like hand-grip strength may should be used as a supportive measure

[a]Appendicular lean mass index by dual-energy absorptiometry (DEXA) or corresponding standards using other body composition methods like bioelectrical impedance analysis (BIA), CT or MRI. Physical examination or standard anthropometric measures like mid-arm muscle or calf circumferences may be also used

and their ability to predict major morbidity after gastrointestinal operations, has been validated in a large cohort of patients [25].

42.4 The Effect of the Gastrointestinal Reconstruction Technique on Gastric Emptying, Resumption of Oral Feeding, and Long-Term Nutritional Status

A Cochrane review [26] comparing pylorus-preserving pancreatoduodenectomy (PPPD) vs. a classic pancreatoduodenectomy procedure (PD) found that delayed gastric emptying, was in favor to the PD procedure. Two [27, 28] studies found a significant difference in favor of PPPD concerning weight gain but not overall quality of life.

In a meta-analysis comparing the outcomes of pancreatico-jejunostomy (PJ) vs. pancreatico-gastrostomy (PG) [29] the authors found no significant difference in the rate of delayed gastric emptying. There was no mention of the timing of resumption of early feeding or long-term nutritional outcomes. In theory, a PG anastomosis should derange intraluminal digestion, because it diverts secretion of pancreatic enzymes and of bicarbonate into the acidic pH of the stomach. Available evidence is based mainly on results from small series of patients. Tomimaru and co-workers [30] found that two years after a PG, the main pancreatic duct dilates slightly more, while atrophy of the remnant pancreatic parenchyma is more severe than after PJ. Other studies with a follow-up of 2 years or less found no difference in symptoms or in performance status after PG versus PJ [31, 32]. In contrast, one study found significantly lower fecal elastase-1 levels, more severe steatorrhea and lower serum level of vitamin D [33] after PG in the long-term. Despite these differences, BMI was unaffected by the type of reconstruction, suggesting that the regimens of enzyme supplementation were effective in preventing severe malabsorption after both operations.

In a systematic review and meta-analysis of differences between single limb vs. dual Roux-en-Y limbs after PD, Klaiber et al. [34] found no significant difference in gastric emptying. There was no mention of the long-term nutritional outcome.

In a meta-analysis [35], gastric emptying was found to be similar between the antecolic and retrocolic anastomosis. Although the study by Park et al. [36] stated that the type of pancreatic surgery influenced the nutritional outcome in multivariate analysis, they did not provide any details or sub-group analyses as to which type of operation (PPPD or PD) or type of gastrointestinal reconstruction was used. Moreover, at 3 months postoperatively, all differences in Global Health Status/ Quality of Life, relative weight loss, and other functional scales had disappeared.

42.5 Safety and Efficacy of Early Oral Feeding

Several meta-analyses on the Enhanced Recovery After Surgery (ERAS) protocol application in pancreatic surgery [37, 38] have demonstrated that early oral feeding after pancreatic surgery is feasible and safe. More challenging to establish is whether early oral feeding is associated with improved outcomes. In a RCT [39], Deng and colleagues reported a statistically significant decrease in delayed gastric emptying (DGE) in the ERAS group. Some studies with a lower level of evidence [10–43] reported conflicting results on delayed gastric emptying with the use of an ERAS protocol. A recent meta-analysis [38] concluded that the incidence of delayed gastric emptying was less in the ERAS group, but this finding was not confirmed by another meta-analysis by Coolsen et al. [37].

There are no convincing data on whether the goal of attaining adequate nutritional needs is speeded up by ERAS protocols. Robertson et al. [44] reported compliance rates of 82% for resumption of oral fluids and 86% for tolerance of the diet. One study [45] showed that the mean daily calorie and protein intake in the first 2 weeks were similar in the ERAS group and the group managed conventionally, despite the fact that during the first 5 post-operative days, the mean daily intakes of calories and proteins favored the ERAS group. In another trial [46], postoperative oral liquids were tolerated by 55% of the patients and solid food in 53%, but compliance decreased substantially in patients with major complications. Nutritional supply using only oral feeding within an ERAS protocol may be insufficient to cover the metabolic demand. Artificial nutritional support should couple oral feeding early postoperatively in malnourished patients, in patients at high risk of developing malnutrition, and in well-nourished patients who do not tolerate at least 50% of their caloric and protein requirement by POD 7. Artificial nutrition should be implemented as soon as possible in those subjects who develop severe complications because of their catabolic effect and possible hindrance to oral food tolerance [22, 23].

Oral intake increases production of pancreatic juice and activation of trypsinogen, which may potentially exacerbate a clinically relevant postoperative pancreatic fistula (CR-POPF). In contrast, early provision of oral intake may decrease catabolism. Fujii et al. [47] analyzed the effect of oral food intake on the healing process of a POPF. In this RCT, they compared a group who were treated with oral dietary intake versus another group of patients who had no oral dietary intake but were maintained on total parenteral nutrition after occurrence of POPF. There were no significant differences between groups in terms of the nutritional indexes at different PODs. As expected, the amount of pancreatic juice from the external drainage tube was greater in oral dietary intake group. Despite this difference in volume of pancreatic drain output, the progression to more clinically-relevant POPF was not statistically different. These data support the concept that oral feeding does not exacerbate POPF in this subset of patients.

One must carefully interpret this finding, however, because the majority of these patients had a biochemical leak without clinical symptoms according to the present ISGPS definition [48].

At present, there is no evidence to show the benefit of avoiding oral intake in patients who are complicated by a CR-POPF after PD or DP, and there are no criteria for who can and who should not be fed orally. Stable patients with a Grade B POPF may well tolerate oral diets, while grade C-POPF severely affects the patient capability to be fed orally [49].

42.6 When to Place a Feeding Tube During Surgery

The likelihood of developing pancreas-specific complications can be predicted by using scoring systems enabling stratification of patients into classes of different risk of developing a POPF [50]. It seems reasonable to suggest placement of a feeding tube in patients with a high risk of POPF (using a Fistula Risk Score ≥ 7 [51]). A further scenario that can affect the decision to place a feeding tube is re-laparotomy. Reoperation after pancreatic resection can be necessary to control postoperative major bleeding, or to drain intraabdominal collections. In patients suffering such life-threatening complication, protein catabolism and severe alterations of carbohydrate and lipid metabolism are often present or may very well develop without nutritional support. Moreover, clinical experience suggest that re-operation may be associated with long interruption of oral feeding and may compromise its early resumption.

42.7 Optimal Route for Post-operative Artificial Nutritional Therapy

Total parenteral nutrition is successful in providing adequate and complete nutritional needs, but this form of nutritional support is associated with many potential complications. Because of the high glucose load needed to deliver an adequate amount of calories, hyperglycemia, metabolic acidosis and fluid overload can occur if not monitored carefully [52].

In contrast, enteral nutrition is more “physiologic”, because the nutrition is delivered directly into the stomach, duodenum, or jejunum. In doing so, enteral nutrition stimulates the release of pancreatobiliary secretions which in combination with the luminal nutrients stimulates the release of metabolic and regulatory gastrointestinal hormones and maintains a more normal gut contractility, blood flow, and mucosal barrier function [53]. Concerns about enteral feeding are that it

may be more difficult to deliver an adequate number of calories and protein, because of low tolerance.

Several studies have compared the use of enteral and parenteral nutrition after pancreatic surgery [22, 23]. In all trials, early enteral nutrition and parenteral nutrition after surgery was given routinely instead of on-demand when early oral feeding is unsuccessful as per the currently recommended ERAS strategy. All but one study [54] favored enteral nutrition because of a lesser incidence of infectious and overall complications, as well as a faster recovery of digestive function, nutritional status and the cost was considerably less. Thus, parenteral nutrition is only recommended in patients in whom adequate amounts of enteral nutrition are not feasible or not tolerated.

42.8 Techniques for Placement of an Enteral Feeding Tube

Gastric feeding may be appropriate, but it can increase the risk of aspiration (e.g., in patients with DGE). In these cases, intrajejunal placement of the feeding tube is strongly indicated [55].

Enteral access can be obtained via insertion of a naso-enteral feeding tube or via more invasive approaches, such as the operative insertion of a feeding jejunostomy at the time of surgery or via a percutaneous or endoscopic gastrostomy with a jejunal extension. Each of these techniques is associated with its own potential complications [56].

With the current interest and use of ERAS protocols, it is questionable whether the routine placement of a jejunostomy is warranted, given the fact that about 50% of patients will require artificial nutritional support after pancreatic surgery, and a naso-jejunal tube can usually be placed postoperatively, if needed [57].

All various techniques for placement of a naso-jejunal feeding tube have their specific disadvantages. Blind placement of feeding tubes beyond the pylorus (in case of PPPD) is frequently unsuccessful and may lead to complications such as inadvertent placement in the bronchus. Therefore, naso-jejunal feeding tubes should be placed with the aid of endoscopic, fluoroscopic or bedside under electromagnetic guidance. A systematic review showed no differences in success and re-insertion rates or complications between these three techniques [58]. The decision on the preferred technique can therefore be made on logistics, costs, and preference of the health care providers.

42.9 Evaluation of Exocrine Pancreatic Function (EPI)

EPI is a *...condition in which the amount of secreted pancreatic enzymes is not enough to maintain normal digestion...* [69].

Table 42.2 Potential mechanisms of post-pancreatectomy maldigestion

1. Loss of pancreatic tissue
2. Loss of hormonal regulation of pancreatic and biliary secretion secondary to the duodenectomy
3. Altered mixing of pancreatic and biliary secretions and gastric emptying
4. Altered intestinal pH
5. Upper gastrointestinal dysmotility
6. Intestinal bacterial overgrowth

After PD, EPI and/or other clinical symptoms of malabsorption can be observed in up to 32% of patients and altered pancreatic function tests are present in up to 80% of patients [59]. EPI was present in 45% at the time of pancreatic cancer diagnosis increasing to 89% after 6 months postoperatively [60]. The onset of post-surgical maldigestion (lack of quantity or mixing of digestive secretions) may be secondary to many potential mechanisms (Table 42.2).

EPI after pancreatic surgery is associated with symptoms related to the presence of undigested food within the intestinal lumen and/or to loss of the absorption of nutrients with subsequent progressive weight loss or fat-soluble vitamins (A, D, E, K) and mineral/electrolyte deficiencies. Patients with EPI often experience debilitating steatorrhea, defaecation urgency, dyspepsia, flatulence, cramping abdominal pain, and nausea; however, overt malabsorptive symptoms are not always apparent in patients with mild/moderate insufficiency [61]. Steatorrhea is defined as presence of more than 7 g/day of fat in the stool [62].

Non-alcoholic fatty liver disease is also being a poorly recognized complication of EPI [63].

If left untreated, EPI has a deleterious impact on nutritional status and on patient quality of life [64]. Abnormal pancreatic exocrine function as evaluated by fecal elastase has been reported as an independent predictor of survival in advanced pancreatic cancer [65].

Steatorrhea generally appears when greater than 90% of the typical secretion of pancreatic enzymes is lost. After PD, the combination of loss of pancreatic tissue and asynchronous mixing of pancreatobiliary secretions with the meal can lead to the onset of steatorrhea also in the presence of a more limited decrease in pancreatic enzyme secretion [66].

Diagnosis of EPI can be difficult in practice. The 72 h-fecal fat collection with a standard intake of fat allows the calculation of the coefficient of fat absorption; this is the gold standard test to diagnose fat malabsorption. But because this test is not available routinely, the fecal elastase-1 (>20 μg/g of stools) may be the only pancreatic function test available in clinical practice [67]. Benini et al. showed that steatorrhea may be present in operated patients even if the fecal elaatase-1 is only mildly decreased [66].

42.10 Pancreatic Enzyme Replacement Therapy (PERT)

Patents who present with symptoms of EPI may be overlooked or advised to adopt inappropriate dietary restrictions in an attempt to control the symptoms. PERT has been shown to stabilize weight, improve dietary intake and decrease daily stool frequency in patients with inoperable pancreatic cancer [67, 68]. PERT use appeared to improve survival in patients post resection in a post-hoc subgroup analysis, predominantly in those with pancreatic ductal dilation [69].

PERT should start with doses of 40,000–50,000 units of lipase with meals, and 10,000–25,000 units with every snack [70, 71]. The dosage need to be carefully monitored, as well as altered, depending on patient food intake/pattern of eating, method of cooking and portion sizes. This will require repeated educational visits concerning alteration of the dosage and timing of administration. Dose escalation and inhibition of gastric acid secretion may be warranted according to response; in patients who fail to respond to treatment, extra-pancreatic causes should be evaluated [5]. Dietary intake and nutritional status should be monitored regularly to maximize patient compliance and specialist dietetic assessment sought in patients with underlying malnutrition. Patients should be encouraged to spread the capsules out over a meal when using multiple capsules or with larger meals. If the patient does not respond to the dosage used, the dosage should be progressively increased since there is no maximum dose or side effects.

There are multiple pancreatic enzyme replacement preparations that are licensed in the United States and European Union. As part of a recent systematic review examining the efficacy of PERT, the authors examined enteric-coated microspheres versus non-coated microspheres with regard to the coefficient of fat absorption and noted a that this was higher with coated microspheres [72].

Table 42.3 summarizes the strength of recommendation and quality of evidence for nutritional support in pancreatic surgery.

42.11 Conclusion

A large body of literature suggests the key role of nutritional support and therapy in affecting short- and long-term outcomes after major pancreatic resections. As any treatment, the benefits are maximized when the indications to the use are appropriate.

Nevertheless, the management of perioperative nutrition in patients undergoing pancreatic surgery is very disparate among surgeons and its benefits often unrewarded. This chapter may help surgeons to acquire awareness on the importance of this therapy and information on the correct indications to nutritional prescription.

Table 42.3 Strength of recommendation and quality of evidence of the statements

	Strength of recommendation	Quality of evidence
Preoperative of the nutritional status, malnutrition risk and anthropometry should be assessed routinely	1	B
Nutritional status and body composition may be affected by neoadjuvant treatments, it is recommended to monitor these parameters regularly and to initiate nutritional counseling and support if needed	1	C
The gastrointestinal reconstruction technique does not affect gastric emptying, resumption of oral feeding, and long-term nutritional status	1	B
Early resumption of oral intake is safe and should be encouraged within ERAS protocols	1	B
Malnourished patients, those at high risk of developing malnutrition, and those who develop severe, post-operative complications early after operation should receive artificial nutrition at once	1	B
Oral intake in clinically stable patients who are complicated by biochemical leakage or grade B POPF is safe, while patients with CR-POPF should be managed on a case-by-case basis	2	C
Placement of a feeding tube for enteral nutrition in patients undergoing PD is recommended in case of:		
1. The patient presents with a severe pre-operative malnutrition	2	B
2. Tthe fistula risk score predicts a high-risk for developing a POPF	1	C
3. In cases of reoperation for major abdominal complications	2	B
Enteral nutrition is preferred over parenteral nutrition when nutritional support is needed	1	A
Presence of EPI should be assessed in all patients undergoing PD	1	C
Untreated EPI and related complications such as weight loss, poor wound healing, deficiencies of fat-soluble vitamins and electrolyte imbalance affect quality of life and oncologic outcomes	1	C
PERT should be initiated routinely in patients after a PD and continued for at least 6 months following surgery	2	B

References

1. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010;362:1605–17.
2. Martin D, Joliat GR, Halkic N, Demartines N, Schäfer M. Perioperative nutritional management of patients undergoing pancreatoduodenectomy: an international survey among surgeons. HPB (Oxford). 2020;22:75–82.
3. Trestini I, Paiella S, Sandini M, Sperduti I, Elio G, Pollini T, et al. Prognostic Impact of Preoperative Nutritional Risk in Patients Who Undergo Surgery for Pancreatic Adenocarcinoma.

Ann Surg Oncol. 2020. https://doi.org/10.1245/s10434-020-08515-5. Epub ahead of print. PMID: 32388740.
4. Cooper C, Burden ST, Molassiotis A. An explorative study of the views and experiences of food and weight loss in patients with operable pancreatic cancer perioperatively and following surgical intervention. Support Care Cancer. 2015;23:1025–33.
5. Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018;164:1035–48.
6. Probst P, Haller S, Bruckner T, Ulrich A, Strobel O, Hackert T, et al. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS pancreas). Br J Surg. 2017;104:1053–62.
7. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539–47.
8. Gianotti L, Sandini M. The 2019 ESPEN Arvid Wretlind lecture perioperative nutritional and metabolic care: Patient-tailored or organ-specific approach?. Clin Nutr. 2020;39:2347–57.
9. Pecorelli N, Capretti G, Sandini M, Damascelli A, Cristel G, De Corbelli F, et al. Sarcopenic obesity is a major determinant of failure to rescue from major complications following pancreaticoduodenectomy: results of a multicenter study. Ann Surg Oncol. 2018;25:308–17.
10. Ozola Zalite I, Zykus R, Francisco Gonzalez M, Saygili F, Pukitis A, Gaujoux S, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology. 2015;15:19–24.
11. Choi Y, Oh DY, Kim TY, Lee KH, Han SW, Im SA, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. PLoS One. 2015;10:e0139749.
12. Sandini M, Pinotti E, Persico I, Picone D, Bellelli G, Gianotti L. Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. BJS Open. 2017;1:128–37.
13. Karagianni VT, Papalois AE, Triantafillidis JK. Nutritional status and nutritional support before and after pancreatectomy for pancreatic cancer and chronic pancreatitis. Indian J Surg Oncol. 2012;3:348–59.
14. Amini N, Spolverato G, Gupta R, Margonis GA, Kim Y, Wagner D, et al. Impact total psoas volume on short- and long-term outcomes in patients undergoing curative resection for pancreatic adenocarcinoma: a new tool to assess sarcopenia. J Gastrointest Surg. 2015;19:1593–602.
15. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg. 2016;264:457–63.
16. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11–48.
17. Cooper AB, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, et al. Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. Ann Surg Oncol. 2015;22:2416–23.
18. Naumann P, Eberlein J, Farnia B, Hackert T, Debus J, Combs SE. Continued Weight Loss and Sarcopenia Predict Poor Outcomes in Locally Advanced Pancreatic Cancer Treated with Chemoradiation. Cancers (Basel). 2019;11:709.
19. Heinrich S, Pestalozzi BC, Schafer M, Weber A, Bauerfeind P, Knuth A, et al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26:2526–31.
20. Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manag. 2012;44:181–91.

21. Sandini M, Patiño M, Ferrone CR, Alvarez-Pérez CA, Honselmann KC, Paiella S, et al. Association between changes in body composition and neoadjuvant treatment for pancreatic cancer. JAMA Surg. 2018;153:1–7.
22. Lobo DN, Gianotti L, Adiamah A, Barazzoni R, Deutz NEP, Dhatariya K, Greenhaff PL, et al. Perioperative nutrition: Recommendations from the ESPEN expert group. Clin Nutr. 2020:S0261-5614(20)30179-5. https://doi.org/10.1016/j.clnu.2020.03.038. Epub ahead of print. PMID: 32362485.
23. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. A.S.P.E.N. Board of Directors, American College of Critical Care Medicine, Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of critical care medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2016;40:159–211.
24. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. Clin Nutr. 2019;38:1–9.
25. Skeie E, Tangvik RJ, Nymo LS, Harthug S, Lassen K, Viste A. Weight loss and BMI criteria in GLIM's definition of malnutrition is associated with postoperative complications following abdominal resections - Results from a National Quality Registry. Clin Nutr. 2020;39:1593–99.
26. Hüttner FJ, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Büchler MW, Diener MK. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev. 2016;2016(2):CD006053.
27. Bloechle C, Broering DC, Latuske C. Prospective randomized study to evaluate quality of life after partial pancreatoduodenectomy according to Whipple versus pylorus preserving pancreatoduodenectomy according to Longmire-Traverso for periampullary carcinoma. Deutsche Gesellschaft fur Chirurgie. 1999;(Supplement 1):661–4.
28. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, et al. Randomized clinical trial of pyloruspreserving duodenopancreatectomy versus classical Whipple resection – long term results. Br J Surg. 2005;92:547–56.
29. Qin H, Luo L, Zhu Z, Huang J. Pancreaticogastrostomy has advantages over pancreaticojejunostomy on pancreatic fistula after pancreaticoduodenectomy. A meta-analysis of randomized controlled trials. Int J Surg. 2016;36:18–24.
30. Tomimaru Y, Takeda Y, Kobayashi S, et al. Comparison of postoperative morphological changes in remnant pancreas between pancreaticojejunostomy and pancreaticogastrostomy after pancreaticoduodenectomy. Pancreas. 2009;38:203–7.
31. Konishi M, Ryu M, Kinoshita T. Pathophysiology after pylorus-preserving pancreoduodenectomy: a comparative study of pancreatogastrostomy and pancreatojejunostomy. Hepato-Gastroenterology. 1999;46:118–26.
32. Jang JY, Kim SW, Park SJ. Comparison of the functional outcome after pylorus-preserving pancreatoduodenectomy: pancreatogastrostomy and pancreatojejunostomy. World J Surg. 2002;26:366–73.
33. Benini L, Amodio A, Cristofori C, Campagnola P, Carestiato F, Davì V, et al. Pancreogastro anastomosis is associated with a more severe derangement of pancreatic function and a more marked reduction of pancreatic volume than pancreojejunal anastomosis. Results of a long-term follow-up study after duodenopancreatectomy. Gastroenterology. 2014;146(Suppl 1):S3–4.
34. Klaiber U, Probst P, Knebel P, Contin P, Diener MK, Büchler MW, Hackert T. Meta-analysis of complication rates for single-loop versus dual-loop (Roux-en-Y) with isolated pancreaticojejunostomy reconstruction after pancreaticoduodenectomy. Br J Surg. 2015;102:331–40.
35. Joliat GR, Labgaa I, Demartines N, Schäfer M, Allemann P. Effect of antecolic versus retrocolic gastroenteric reconstruction after pancreaticoduodenectomy on delayed gastric emptying: a meta-analysis of six randomized controlled trials. Dig Surg. 2016;33:15–25.

36. Park JW, Jang JY, Kim EJ, Kang MJ, Kwon W, Chang YR, et al. Effects of pancreatectomy on nutritional state, pancreatic function and quality of life. Br J Surg. 2013;100:1064–70.
37. Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. World J Surg. 2013;37:1909–18.
38. Xiong J, Szatmary P, Huang W, de la Iglesia-Garcia D, et al. Enhanced recovery after surgery program in patients undergoing pancreaticoduodenectomy. A PRISMA-compliant systematic review and meta-analysis. Medicine. 2016;18(95):1–10.
39. Deng X, Cheng X, Huo Z, Shi Y, et al. Modified protocol for enhanced recovery after surgery is beneficial for Chinese cancer patients undergoing pancreaticoduodenectomy. Oncotarget. 2017;18:47841–8.
40. Kennedy EP, Grenda TR, Sauter PK, Rsato EL, et al. Implementation of a critical pathway for distal pancreatectomy at an academic institution. J Gastrointest Surg. 2009;13:938–44.
41. Balzano G, Zerbi A, Braga M, Rocchetti S, et al. Fast-track recovery programme after pancreaticoduodenectomy reduces delayed gastric emptying. Br J Surg. 2008;95:1387–93.
42. Abu Hilal M, Di Fabio F, Badran A, Alsaati H, et al. Implementation of enhanced recovery programme after pancreaticoduodenectomy: a single-centre UK pilot study. Pancreatology. 2013;13:58–62.
43. Coolsen MME, van Dam R, Chigharoe A, Olde Damink SWM, et al. Improving outcome after pancreaticoduodenectomy: experiences with implementing an Enhanced Recovery After Surgery (ERAS) program. Dig Surg. 2014;31:177–84.
44. Robertson N, Gallacher PJ, Peel N, Garden OJ, et al. Implementation of an enhanced recovery programme following pancreaticoduodenectomy. HPB. 2012;14:700–8.
45. Hwang SE, Jung MJ, Cho HB, Yu HC. Clinical feasibility and nutritional effects of early oral feeding after pancreaticoduodenectomy. Korean J Hepatobiliary Pancreat Surg. 2014;18:84–9.
46. Braga M, Pecorelli N, Ariotti R, Capretti G, et al. Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. World J Surg. 2014;38:2960–6.
47. Fujii T, Nakao A, Murotani K, Okamura Y, Ishigure K, Hatsuno T, et al. Influence of food intake on the healing process of postoperative pancreatic fistula after pancreatoduodenectomy: a multi-institutional randomized controlled trial. Ann Surg Oncol. 2015;22:3905–12.
48. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2017;161:584–91.
49. Berry AJ. Pancreatic surgery: indications, complications, and implications for nutrition intervention. Nutr Clin Pract. 2013;28:330–57.
50. Sandini M, Malleo G, Gianotti L. Scores for prediction of fistula after pancreatoduodenectomy: a systematic review. Dig Surg. 2016;33:392–400.
51. Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013;216:1–14.
52. Torgersen Z, Balters M. Perioperative nutrition. Surg Clin North Am. 2015;95:255–67.
53. Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignancy. Arch Surg. 1997;132:1222–30.
54. Perinel J, Mariette C, Dousset B, et al. Early enteral versus total parenteral nutrition in patients undergoing pancreaticoduodenectomy: a randomized multicenter controlled trial (Nutri-DPC). Ann Surg. 2016;264:731–7.
55. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. Crit Care. 2003;7:R46–51.
56. Gerritsen A, Besselink MG, Gouma DJ, et al. Systematic review of five feeding routes after pancreatoduodenectomy. Br J Surg. 2013;100:589–98.

57. Gerritsen A, Wennink RAW, Busch ORC, et al. Feeding patients with preoperative symptoms of gastric outlet obstruction after pancreatoduodenectomy: early oral or routine nasojejunal tube feeding? Pancreatology. 2015;15:548–53.
58. Gerritsen A, van der Poel MJ, de Rooij T, et al. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic placement of nasoenteral feeding tubes. Gastrointest Endosc. 2015;81:836–47.
59. Sabater L, Ausania F, Bakker OJ, Boadas J, Domínguez-Muñoz JE, Falconi M, et al. Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery. Ann Surg. 2016;264:949–58.
60. Sikkens EC, Cahen DL, de Wit J, et al. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. Br J Surg. 2014;101:109–13.
61. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Gastroenterol Hepatol (NY). 2011;7:401–3.
62. Tran TC, van Lanschot JJ, Bruno MJ, van Eijck CH. Functional changes after pancreatoduodenectomy: diagnosis and treatment. Pancreatology. 2009;9:729–37.
63. Tanaka N, Horiuchi A, Yokoyama T, Kaneko G, Horigome N, Yamaura T, et al. Clinical characteristics of de novo nonalcoholic fatty liver disease following pancreaticoduodenectomy. J Gastroenterol. 2011;46:758–68.
64. Bachmann K, Tomkoetter L, Kutup A, et al. Is the Whipple procedure harmful for long-term outcome in treatment of chronic pancreatitis? 15-years follow-up comparing the outcome after pylorus-preserving pancreatoduodenectomy and Frey procedure in chronic pancreatitis. Ann Surg. 2013;258:815–20.
65. Partelli S, Frulloni L, Minniti C, Bassi C, Barugola G, D'Onofrio M, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. Dig Liv Dis. 2012;44:945–95.
66. Benini L, Amodio A, Campagnola P, Agugiaro F, Cristofori C, Micciolo R, et al. Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. Pancreatology. 2013;13:38–42.
67. Stein J, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. Clin Chem. 1996;42:222–6.
68. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998;42:92–6.
69. Roberts KJ, Schrem H, Hodson J, Angelico R, Dasari BVM, et al. Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy. HPB (Oxford). 2017;19:859–67.
70. Imrie CW, Connett G, Hall RI, Charnley RM. Review article: enzyme supplementation in cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer. Aliment Pharmacol Ther. 2010;32(Suppl 1):1–25.
71. Löhr JM, Oliver MR, Frulloni L. Synopsis of recent guidelines on pancreatic exocrine insufficiency. United European Gastroenterol J. 2013;1:79–83.
72. de la Iglesia-García D, Huang W, Szatmary P, Baston-Rey I, Gonzalez-Lopez J, Prada-Ramallal G, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut. 2017;66:1354–5.

Chapter 43
Management of Pancreatic Exocrine Insufficiency

Sarah Powell-Brett, Ruth Chinuck, and Keith Roberts

Take Home Message

- Symptoms of pancreatic exocrine insufficiency can be vague and are often mistakenly attributed to the underlying cancer. Furthermore, it follows a progressive course with approximately 10% loss in function per month.
- Consider prescribing pancreatic enzyme replacement therapy for all patients with pancreatic cancer even in the absence of a diagnostic test.
- Dietician involvement ensures regular, long-term clinical, dietary, anthropometric and biochemical evaluation, invaluable in the management of pancreatic exocrine insufficiency

Pearls and Pitfalls

- Screen regularly for type 3c diabetes and micronutrient deficiencies.
- The current widely used diagnostic test, faecal elastase, has relatively poor accuracy, particularly post pancreatoduodenectomy.
- Pancreatic enzymes are dependent on a neutral or near neutral pH to be effective, consider the addition of a proton pump inhibitor.

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43.1 Introduction

Many factors contribute to weight loss and malnutrition in pancreatic cancer; the most significant being pancreatic exocrine insufficiency (PEI). Optimising nutritional status is imperative to survival and to enable patients to withstand treatment and maintain a good quality of life. In unresectable pancreatic cancer, the incidence of PEI is reported between 66% and 92% [1].

Following surgical resection, it is more difficult to assess the true incidence of PEI because of the heterogeneity of studies and the variable diagnostic standards (faecal elastase-1 being a common way of assessing function yet its accuracy is adversely affected resection). Evaluation of PEI in patients with pancreatic cancer before and after pancreaticoduodenectomy to determine the prevalence of PEI found 44% before surgery and 74% (range 36–100%) after surgery [2].

It is also essential to recognise that PEI is a dynamic, and generally progressive, disease state. A 2007 retrospective review with a longer follow up of 52 months after pancreatoduodenectomy found that 100% of patients had PEI by this time, and a prospective cohort study assessing PEI at multiple time points after diagnosis found that 66% of patients had PEI at the time of diagnosis and 92% had PEI within 2 years of diagnosis [1, 3]. Among patients with unresectable disease there is a 10% decline in pancreatic exocrine function per month [1].

43.1.1 Pathophysiology of Exocrine Insufficiency

It is important to understand that the functional capacity does not just rely on the ability of the pancreas to secrete enzymes but on the capacity of those enzymes to get to the right place, at the right time and at the correct pH in order to perform their digestive function. Thus, the term pancreatic exocrine insufficiency in a clinical context refers to the digestive ability of the pancreas, not just the secretory output. There are several contributing factors to PEI aside from loss of parenchymal function (Table 43.1).

Table 43.1 Factors contributing to pancreatic exocrine insufficiency in pancreatic cancer

Irresectable or pre-operative setting	Resected[a]
Pancreatic duct obstruction preventing enzyme flow	Resection of pancreatic tissue
Direct damage to pancreatic parenchyma reducing enzyme secretion	Duodenal resection reducing CCK induced post prandial enzyme secretion
Pancreatic duct obstruction preventing bicarbonate flow with subsequent failure to neutralise the pH of small bowel content	Asynchrony between pancreatic secretion and gastric emptying
	Reconstruction delivering enzymes into a more acidic environment with less enterokinase

[a]Pancreatoduodenectomy or total pancreatectomy

There are multiple contributing factors to PEI in pancreatic cancer (Fig. 43.1). For both operable and inoperable disease there may be direct damage to the acini and obstruction of the pancreatic ducts preventing the passage of secretions. Bicarbonate is secreted solely by the pancreas and neutralises gastric acid. Thus, obstruction leads not only to a reduction in enzyme secretion but a reduction in the ability to normalise the luminal pH of small bowel. This reduces the function of exogenous or endogenous pancreatic enzymes. For operated pancreatic cancer there is physical loss of pancreatic tissue compounded by anatomical and physiological changes that reduce the enzymatic function. Duodenal resection results in a reduction in the intestinal phase of secretion (CCK mediated), in addition, the reconstructive element results in pancreatic enzymes reaching a more distal part of small intestine that is less rich in enterokinase (reducing enzyme activation) and more acidic (inactivating digestive enzymes). This is best demonstrated by the differences in PEI with different forms of reconstruction: An evaluation of exocrine function following pancreaticoduodenectomy in 99 patients found pancreaticogastrostomy to be an independent risk factor for exocrine insufficiency and a retrospective review of PEI (based on PERT usage) after pancreaticoduodenectomy found significantly higher rates of PEI in the pancreaticogastrostomy group when compared to pancreatojejunostomy (75% compared to 46% had PEI at 1 year after surgery, respectively, $p < 0.001$) [4, 5].

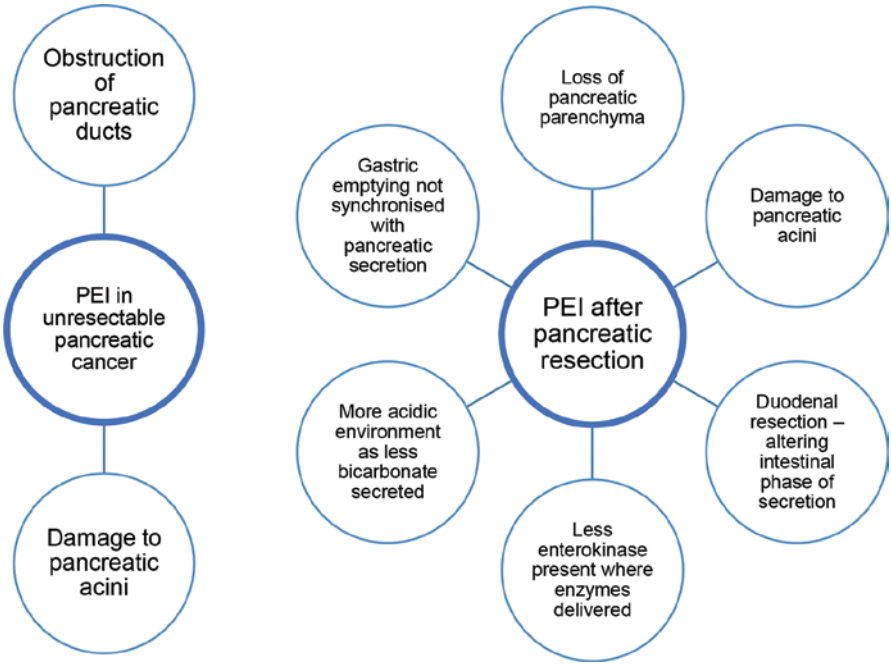

Fig. 43.1 Factors contributing to pancreatic exocrine insufficiency in pancreatic cancer

43.2 Diagnosis of Pancreatic Exocrine Insufficiency in Pancreatic Cancer

This section focuses on the currently available tests for PEI relevant to pancreatic cancer. An effective diagnostic test for PEI is essential to assess the need for, correct dosage of, and efficacy of pancreatic enzyme replacement therapy (PERT), in order to prevent the effects of maldigestion.

PEI should be considered a digestive disorder rather than a secretory disorder. This is important when considering the diagnosis of PEI in pancreatic cancer as testing can be direct (measuring the secretory capacity of the pancreas) or indirect (measuring the digestive effect of pancreatic enzymes). See Table 43.2 for the advantages and disadvantages of the most widely used diagnostic tests.

43.2.1 Secretin-Pancreozymin Test

The most accurate direct test is the secretin-pancreozymin test which measures enzyme output after pancreatic stimulation via collection of duodenal secretions from a tube sited in the duodenum. These tests are not translatable into routine clinical use, as they are invasive, costly, time consuming, require specialist equipment and training, and carry some risk of harm. They are therefore largely limited to research or complex cases. Faecal elastase 1 (FE-1) is the most widely

Table 43.2 Advantages and disadvantages of currently available tests of pancreatic function

	Advantages	Disadvantages
Secretin-pancreozymin test	– Most sensitive test for the secretory capacity of the pancreas – Can classify severity	– Costly – Time consuming – Invasive – Not widely available – Poorly standardised
72-h faecal fat quantification	– Gold standard for quantifying steatorrhea	– Unpleasant – Time consuming – Must stop PERT – Limited sensitivity for mild/moderate PEI
Faecal elastase (FE-1)	– 73–100% sensitivity for severe PEI – Cost effective – Easy to perform	– Limited use post pancreatic surgery – 0–63% sensitivity for mild PEI – Limited specificity with watery stool
13C-MTG test	– >90% sensitivity for detecting fat maldigestion – Good for estimating the effect of PERT	– Limited sensitivity in mild pancreatic dysfunction – Not widely available outside tertiary centres – Time consuming

used direct test (both in research and clinical environments); it is easy to perform, does not require specialist facilities, and is relatively cheap [6]. With severe PEI, the reported sensitivity ranges between 73% and 100% and with mild insufficiency between 0% and 63% [7, 8]. It also has limited specificity in watery stools and is unreliable for assessing PEI in patients after pancreatic surgery [8, 9].

43.2.2 Faecal Fat Quantification

The reference standard of PEI evaluation is faecal fat quantification, requiring 72-h collection of faeces and determination of the coefficient of fat absorption (CFA). More than 7 g of fat per 100 g stool per day diagnoses fat malabsorption and more than 15 g diagnoses severe steatorrhea [10]. It is a good measure of the capacity for fat digestion, but is unpleasant and time consuming for both patients and laboratory staff alike (requiring strict adherence to 100 g of fat per day diet for 5 days and all faeces to be collected over 3 days), it is of limited use in mild PEI and is not specific for pancreatic disease. Thus this test is now largely reserved for research purposes [11].

43.2.3 Breath Tests

Several breath tests have been evaluated for use in the diagnosis of PEI, the most promising of which is the ^{13}C mixed triglyceride breath test (^{13}CMTGT) ^{13}C labelled fatty substrates are digested by lipolysis (using pancreatic secretion of lipase). The free fatty acids and monoglycerol released are absorbed and oxidised by the liver to $^{13}CO_2$, which is then exhaled. The most variable step along this process is the enzymatic breakdown of the substrate in proximal small bowel. The increase in the concentration of $^{13}CO_2$ in the breath thus correlates with the secretion of pancreatic lipase. The ^{13}CMTGT is non-invasive, relatively easy to perform, and the result is not affected by watery stool, making it more widely acceptable and specific than the CFA test. Significantly, it reflects the entire process of digestion and absorption, not just the secretion of enzymes and thus more useful after pancreatic resection. A proposed optimal breath test with the administration of 250 mg of ^{13}CMTG together with a solid test mean containing 16 g of fat after an overnight fast found that the ^{13}CMTGT correlated well with CFA testing with a sensitivity of 93% and a specificity of 92% for the diagnosis of PEI [12]. The main drawback is the timeframe for testing being 6 h and the requirement for the administration of ^{13}C-MTG making it of limited routine use.

In clinical practice the diagnosis of PEI is based on a combination of probability (high incidence of PEI in both inoperable and operable pancreatic cancer), clinical suspicion, and may be supported by a diagnostic test (with FE-1 being most

commonly used as it is routinely available and acceptable). With no functional test widely available for routine use at present, the current approach to this group of patients is to treat without testing if there is clinical suspicion.

43.3 Consequences of PEI in Adults with Pancreatic Cancer

Symptoms manifest when ingested food overwhelms the functional capacity of the pancreas (through any of the mechanisms described above) and can have a significant impact on the daily lives of patients and their carers. The symptoms of PEI are subtle and often confused with other disease states such as the underlying cancer; for example, weight loss and abdominal discomfort are invariably associated with PEI. Classical signs such as steatorrhoea are associated with severe PEI and furthermore patients may modify their diet, often subconsciously, to reduce the burden of their symptoms. Many patients can exhibit significant malabsorption with an absence of abdominal symptoms, especially if fat intake has been reduced in an attempt to help alleviate symptoms [13]. Symptoms and signs are summarised in Table 43.3.

By the time of diagnosis, over 80% of patients with pancreatic cancer have lost weight and over a third of these patients have lost >10% of their body weight [14]. The consequence of the resultant nutritional deficiencies can be extensive; PEI has been shown to increase the risk of osteoporosis, cardiovascular events, sarcopenia and even shorten survival [15–17].

Post pancreatic resection, PEI has been associated with increased costs, higher post-operative complications and longer inpatients stays [18–21].

Considering the above, it is imperative to maintain normal digestion and nutritional status, this requires intensive, specialist dietetic support as part of a

Table 43.3 Signs and symptoms of pancreatic exocrine insufficiency [13]

Signs and symptoms of PEI	
Steathorrhoea	Malnutrition
Loose watery stool	Weight loss (often despite good oral intake)
Undigested food in stools	Vitamin deficiencies (especially A, D, E, K)
Post-prandial abdominal pain	Hypoglycaemia in diabetes
Nausea/colicky abdominal pain	
Gastro-oesphageal reflux	
Bloating/flatulence	
Offensive smelling wind/stools	
Indigestion	
Anorexia	
Early satiety	

multi-professional team. This ensures regular, long-term clinical, dietary, anthropometric and biochemical assessments to assist in the evaluation of exocrine insufficiency [13, 22].

43.4 Nutritional Evaluation

The diagnosis of PEI is challenging. Altered nutritional status is the main consequence of PEI. Given the failings of available diagnostic tests the ultimate assessment of PEI is to combine the results of diagnostic tests (typically FE-1) with symptoms, biochemistry and the response of any abnormal results/symptoms to treatment. This comprehensive review requires specialist knowledge, expertise and time [23]. Therefore, part of the evaluation of PEI should include a dietetic assessment carried out by Specialist Dietitian experienced and skilled in PEI.

This should include regular screening for Type 3c diabetes and micronutrient deficiencies. Type 3 or pancreatogenic diabetes develops due to the loss of pancreatic parenchyma. It differs from type 2 diabetes in that patients continue to have normal or enhanced peripheral insulin sensitivity [24]. Causes of pancreatogenic diabetes include pancreatic resection or damage caused by neoplasms [25]. Of note, several studies suggest a tumour associated paraneoplastic mechanism inducing diabetes in pancreatic cancer, for example β cell de-differentiation and dysfunction [26, 27]. Prevalence of type 3 diabetes amongst patients with PDAC is as high as 47% [28]. In addition, routine vitamin and mineral supplementation may also be recommended [13]. Whilst, the recommendations are not based on direct evidence and warrant further investigation/validation, a regimen for the screening (e.g pre-pancreatic resection) and surveillance of malnutrition is proposed (Table 43.4).

43.5 Quality of Life

Overall, the aims of nutritional management are to maintain or improve quality of life [22]. Pancreatic enzymes particularly provide relief of maldigestion-related symptoms and normalise the nutritional status of patients. However, many patients are undiagnosed or under-treated which leads to worsening symptoms, reduced health-related quality of life and potentially increased malnutrition-related morbidity and mortality [29]. Therefore, a patient reported outcome tool is a valuable way of standardizing assessment and quantifying disease specific burden of PEI.

The Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q), evaluated in 2019, is the first PEI specific patient reported outcome measure [29]. It was designed to assess PEI in patients with mild, moderate and severe symptoms and the impact on health-related quality of life, alongside the Bristol stool form scale [29]. Further work is needed to assess the utility of this tool in academic and clinical practice.

Table 43.4 Proposed approach to the practical evaluation of PEI in clinical practice [13, 23]

Test	Screening	Baseline	Surveillance
Fat soluble vitamin status	Serum alpha tocopherol (vitamin E) and if abnormal (low) move to baseline tests	Within 1 year after surgical resection or sooner if the patient has signs and symptoms of malabsorption: Serum retinol, 25-OH vitamin D, alpha tocopherol, vitamin K status (e.g. PT)	Normal baseline test: annually Abnormal: attempt correction and recheck in 3 months
Other micronutrients (copper, zinc and selenium)	–	Within 1 year after surgical resection or sooner if the patient has signs and symptoms of malabsorption	Normal baseline test: annually Abnormal: attempt correction and recheck in 3 months
Anaemia screen	Serum ferritin, haemoglobin, c-reactive protein	Within 1 year after surgical resection or sooner if the patient has signs and symptoms of malabsorption: Iron studies, e.g. full blood count, folate, vitamin B12	Normal baseline test: annually Abnormal: attempt correction and recheck in 3 months: Iron studies, e.g. full blood count, folate, vitamin B12
Consequences of ongoing diahorrea (only if symptomatic)	Magnesium	Within 1 year after surgical resection or sooner if the patient has signs and symptoms of malabsorption: magnesium, potassium	Normal baseline test: annually Abnormal: attempt correction and recheck in 3 months: magnesium, potassium
Bone profile and Bone mineral density	–	After completion of surgical recovery and any adjuvant treatment, within 2 years post operatively: Corrected Calcium, phosphate and parathyroid hormone, dual-energy X-ray absorptiometry	Normal baseline test: every 5 years Abnormal: attempt correction and recheck in 3 months
Glycaemic control	Non diabetic: Random glucose Diabetic: Incidence of hypoglycaemia, HbA1c	Annual OGTT (people without diabetes) Diabetic: Incidence of hypoglycaemia, HbA1c	Annual OGTT (people without diabetes) Diabetic: Incidence of hypoglycaemia, HbA1c
Plasma proteins	Retinol binding protein, albumin, prealbumin	–	–

PT pro-thrombin time, *OGTT* oral glucose tolerance test, *HbA1c* glycosolated haemoglobin

43.6 Pancreatic Exocrine Replacement Therapy (PERT) in Pancreatic Cancer

Given the prevalence of PEI in pancreatic cancer and the fundamental importance of nutrition, PERT is an essential component of pancreatic cancer care. This is reflected by the National Institute of Clinical Excellence in the United Kingdom recommending PERT for all patients. PERT is known to improve the absorption of fats and protein and reduces stool fat which improves quality of life [30]. In a small randomised trial, patients with unresectable cancer who received PERT maintained their dietary intake and weight whilst those on placebo lost weight and had worse intake of nutrition [31].

More recently, the effects on survival have been observed. In an observational cohort study of 469 patients undergoing pancreatoduodenectomy for cancer, patients on PERT survived 6.4 months longer than patients without [32]. In the study, the use of PERT was associated with improved survival in multivariate and propensity matched models. Furthermore, when patients were stratified by their pancreatic duct width (as a surrogate for exocrine insufficiency) benefit was markedly different among those with a dilated pancreatic duct (3 mm or greater) where the median survival was 1.5 years greater among those receiving PERT than those that did not [32].

Among patients with unresectable cancer Dominguez-Munoz et al. demonstrated a survival advantage when patients received PERT. In that study those patients receiving PERT also received more chemotherapy [33]. It could therefore be argued that any survival advantage may have been attributed to chemotherapy and not PERT. However, causation is not clear, and it may be that PERT enabled those patients to receive chemotherapy.

In a population based propensity-matched cohort study the use of PERT was associated with greater survival among the entire cohort and those with unresectable cancer regardless of whether they did or did not receive chemotherapy suggesting that PERT use directly improves the duration of survival [34]. In that study, however, the proportion of long term survivors was not different suggesting that whilst PERT is associated with an increased duration of survival, it does not contribute to an increase in overall survival. The survival time ratio was 262% greater among those receiving PERT than matched controls; this benefit was of a similar magnitude to that of chemotherapy or surgery confirming the essential role that PERT has, and that of correcting PEI/malnutrition, among patients with pancreatic cancer.

43.6.1 Use of Replacement Therapy in Practice

Although there is an increasing evidence base of benefit for PERT and understanding of the incidence of PEI in pancreatic cancer it is somewhat surprising that PERT is underused. Within the UK population-based cohort study PERT use was 21.7%

(study cohort 1998–2015). There is evidence of an increase in use of PERT, however; the RICOCHET UK national prospective audit of pancreatic cancer (2018) demonstrated that some 50% of patients received PERT [35]. Under treatment has been reported in other European countries (2012) and just 21% of Australian patients with unresectable cancer and symptoms of malabsorption received PERT in a study published in 2016 [36, 37].

Exact barriers to treatment with PERT are unclear but likely contributed to by the vague symptoms of PEI, many of which are confused with effects of the underlying cancer i.e. weight loss and abdominal pain and of a diagnostic test that lacks both efficacy and a rapid result. Assays determining faecal elastase levels are the standard diagnostic test however as highlighted above it has limited accuracy and furthermore, unlike blood or urine tests which can be collected on hospital visits stool samples need to be returned to the hospital. Clinicians therefore need to remember to review this test and act upon it. Consequently, results will be available only weeks after the initial request for faecal elastase. Further limitations of the test are that it cannot be used to assess response to treatment or to adjust dosing of PERT. The inclusion of a dietician within a team is considered essential to ensure that PEI, PERT and responses to treatment are optimised.

43.6.2 Adjuncts to Treatment

A proton pump inhibitor is often prescribed with PERT [38]. Endo- and exogenous pancreatic enzymes are very dependent upon a neutral or near neutral pH to be effective. Gastric acid released to the duodenum and small bowel is ordinarily neutralised by bicarbonate secreted from the pancreas. However, in cases of duct obstruction, bicarbonate secretion is impeded. After surgery, particularly pancreatoduodenectomy, mechanisms of normal pancreatic stimulation (cholecystokinin, VIP, vagal stimulation) are largely lost leading to not only reduced enzyme production but also reduced bicarbonate production. It is thus important to prescribe drugs that suppress gastric acid as these help normalise the pH of small bowel content. There is also evidence that proton pump inhibitors maintain pancreatic volume after pancreatoduodenctomy through a mechanism that involves increased levels of gastrin [39].

43.7 Treatment of PEI and of Unresolved Symptoms of PEI When on PERT

Patients should be commenced on 50,000–75,000 units of lipase with meals and 25,000–50,000 units of lipase with snacks, milky drinks and nutritional supplements [13]. Patients should be reviewed after two weeks and if symptoms are not

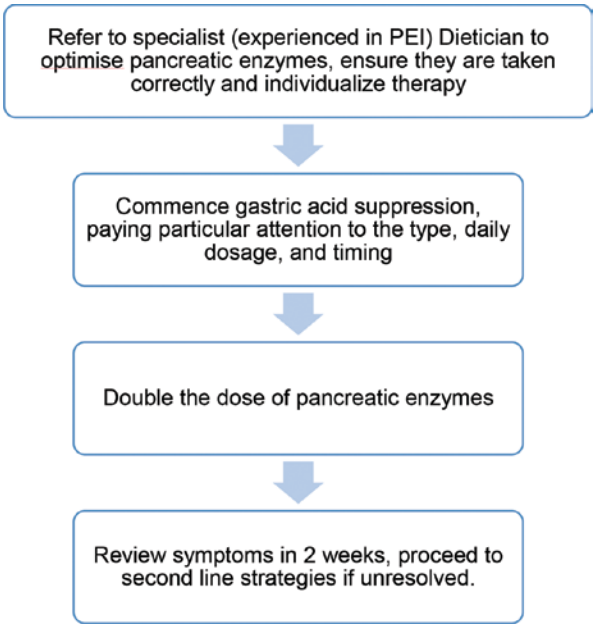

Fig. 43.2 First line response to unresolved symptoms of pancreatic exocrine insufficiency in pancreatic cancer patients (operated or not-operated) [13]

controlled, then other reasons should be assessed such as insufficient dosing, lack of compliance, inadequate timing and education around the importance of pancreatic enzymes (see Fig. 43.2 for a summary of this approach) [40, 41]. If there is a continued poor response despite this initial review a more complex approach to the patient is needed.

43.7.1 After Pancreatic Head Surgery

Following pancreaticoduodenectomy, the reconstruction predisposes patients to bile salt malabsorption and small bowel bacterial overgrowth. Bile salt malabsorption following pancreatic resection may be attributed to concurrent cholecystectomy or the binding of bile salts to mal-digested protein, carbohydrates and fibre. Precipitation of bile salts may occur due to the change in pH in the small bowel as a result of reduced bicarbonate secretion secondary to diminished pancreatic volume [13]. Symptoms of bile salt malabsorption include longstanding steatorrhea, urgency, faecal incontinence, flatulence, abdominal pain, bloating and nocturnal defecation. The management of bile acid malabsorption should include referral to a gastroenterologist for SeCHat (tauroselcholic [75 selenium] acid) study and trial of a bile acid sequestrant (such as Colesevelam) [42].

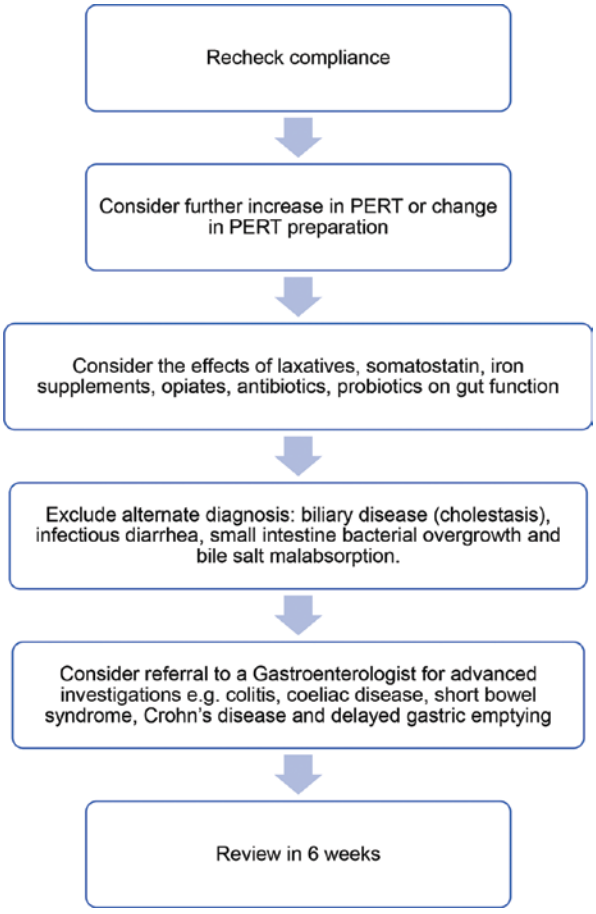

Fig. 43.3 Second line response if symptoms continue despite first line considerations [13, 44]

The presence of a blind loop of bowel within the reconstruction following pancreatoduodenectomy predisposes patients to small intestine bacterial overgrowth (SIBO). The most common symptoms associated with this include diarrhea, flatulence, abdominal pain and bloating. The management of small intestine bacterial overgrowth should include referral to a gastroenterologist for breath tests which are widely used as an alternative to direct jejunal aspiration because they are noninvasive and less expensive. Treatment for SIBO is complex and must be individualized. The three main components are to treat the underlying disease or condition, eradicate overgrowth and address associated nutritional deficiencies. Alongside this antibiotic treatment which should selectively target those bacterial strains that cause SIBO [43]. A thorough description is outside the remit of this work but the proposed algorithm provides clinicians with an evidence based and pragmatic approach to managing these patients (Fig. 43.3).

43.8 Conclusion

To conclude, PEI poses a significant problem for patients with pancreatic cancer, not only for quality of life, but also for the related morbidity. Pancreatic enzyme replacement therapy is essential to maintaining adequate nutrition, improving quality of life and confers a survival advantage yet there is evidence that it is under prescribed across Europe. As a widely available, functional test is not in routine practice, a “treat all’ approach to patients with pancreatic cancer is advisable. The involvement of a dietician is invaluable to the .long-term care of patients with pancreatic cancer.

References

1. Sikkens EC, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol. 2014;48:e43–6.
2. Tseng DS, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas. 2016;45:325–30.
3. Nordback I, Parviainen M, Piironen A, Raty S, Sand J. Obstructed pancreaticojejunostomy partly explains exocrine insufficiency after pancreatic head resection. Scand J Gastroenterol. 2007;42:263–70.
4. Roeyen G, Jansen M, Ruyssinck L, et al. Pancreatic exocrine insufficiency after pancreaticoduodenectomy is more prevalent with pancreaticogastrostomy than with pancreaticojejunostomy. A retrospective multicentre observational cohort study. HPB (Oxford). 2016;18:1017–22.
5. Hirono S, Murakami Y, Tani M, et al. Identification of risk factors for pancreatic exocrine insufficiency after pancreaticoduodenectomy using a 13C-labeled mixed triglyceride breath test. World J Surg. 2015;39:516–25.
6. Chowdhury RF, C. Reveiw article: pancreatic funciton testing. Aliment Pharm Ther. 2002;17:733–50.
7. Laterza LS, Bruno G, Agnes A, Boskoski I, Ianiro G, Geradi V, Ojetti V, Alfieri S, Gasbarrini A. Pancreatic function assesment. Eur Rev Med Pharmacol Sci. 2013;17:65–71.
8. Dominguez-Munoz JE, Lerch MM, Lohr MJ. Potential for screening for pancreatic exocrine insufficiency using the fecal elastase-1 test. Dig Dis Sci. 2017;62:1119–30.
9. Benini L, Amodio A, Campagnola P, et al. Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. Pancreatology. 2013;13:38–42.
10. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol. 2013;19:7258–66.
11. Ii JGL, Draganov PV. Pancreatic function testing: here to stay for the 21st century. World J Gastroenterol. 2008;14:3149–58.
12. Dominguez-Munoz JE, Nieto L, Vilarino M, Lourido MV, Iglesias-Garcia J. Development and diagnostic accuracy of a breath test for pancreatic exocrine insufficiency in chronic pancreatitis. Pancreas. 2016;45:241–7.
13. Phillips ME. Pancreatic exocrine insufficiency following pancreatic resection. Pancreatology. 2015;15:449–55.
14. Gilliland TM, Villafane-Ferriol N, Shah KP, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients. 2017;9:243.

15. Sikkens EC, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. Pancreatology. 2013;13:238–42.
16. Shintakuya R, Uemura K, Murakami Y, et al. Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease. Pancreatology. 2017;17:70–5.
17. de la Iglesia D, Vallejo-Senra N, Lopez-Lopez A, et al. Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: a prospective, longitudinal cohort study. J Gastroenterol Hepatol. 2019;34:277–83.
18. Partelli S, Frulloni L, Minniti C, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. Digest Liver Dis. 2012;44:945–51.
19. Gooden HM, White KJ. Pancreatic cancer and supportive care—pancreatic exocrine insufficiency negatively impacts on quality of life. Support Care Cancer. 2013;21:1835–41.
20. van Dijk SM, Heerkens HD, Tseng DSJ, Intven M, Molenaar IQ, van Santvoort HC. Systematic review on the impact of pancreatoduodenectomy on quality of life in patients with pancreatic cancer. HPB (Oxford). 2018;20:204–15.
21. Heerkens HD, van Berkel L, Tseng DSJ, et al. Long-term health-related quality of life after pancreatic resection for malignancy in patients with and without severe postoperative complications. HPB (Oxford). 2018;20:188–95.
22. Todorovic VM. A pocket guide to clinical nutrition. 5th ed. Birmingham: Parenteral and Enteral Nutrition Specialist Group of the British Dietetic Association; 2018.
23. Lindkvist B, Phillips ME, Dominguez-Munoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: Prevalence and diagnostic use. Pancreatology. 2015;15:589–97.
24. Burkhart RA, Gerber SM, Tholey RM, et al. Incidence and severity of pancreatogenic diabetes after pancreatic resection. J Gastrointest Surg. 2015;19:217–25.
25. Petzel MQB, Hoffman L. Nutrition implications for long-term survivors of pancreatic cancer surgery. Nutr Clin Pract. 2017;32:588–98.
26. Javeed N, Sagar G, Dutta SK, et al. Pancreatic cancer-derived exosomes cause paraneoplastic beta-cell dysfunction. Clin Cancer Res. 2015;21:1722–33.
27. Wang Y, Ni Q, Sun J, et al. Paraneoplastic beta cell dedifferentiation in non-diabetic patients with pancreatic cancer. J Clin Endocrinol Metab. 2019;105(4):dgz224.
28. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes. 2017;66:1103–10.
29. Johnson CD, Williamson N, Janssen-van Solingen G, et al. Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). Pancreatology. 2019;19:182–90.
30. Seiler CM, Izbicki J, Varga-Szabo L, et al. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. Aliment Pharmacol Ther. 2013;37:691–702.
31. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998;42:92–6.
32. Roberts KJ, Schrem H, Hodson J, et al. Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy. HPB. 2017;19:859–67.
33. Dominguez-Munoz JE, Nieto-Garcia L, Lopez-Diaz J, Larino-Noia J, Abdulkader I, Iglesias-Garcia J. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: a retrospective analysis. BMC Cancer. 2018;18:534.
34. Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study. Pancreatology. 2019;19:114–21.
35. JMIR. Receipt of curative resection or palliative care for hepatopancreaticobiliary tumours (RICOCHET): protocol for a nationwide collaborative observational study. JMIR Res Protoc. 2019;8:e13566.

36. Sikkens EC, Cahen DL, van Eijck C, Kuipers EJ, Bruno MJ. The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery: a northern European survey: enzyme replacement after surgery. J Gastrointest Surg. 2012;16:1487–92.
37. Landers A, Muircroft W, Brown H. Pancreatic enzyme replacement therapy (PERT) for malabsorption in patients with metastatic pancreatic cancer. BMJ Support Palliat Care. 2016;6:75–9.
38. Dominguez-Munoz JE, Iglesias-Garcia J, Iglesias-Rey M, Vilarino-Insua M. Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. Gut. 2006;55:1056–7.
39. Jang JY, Kim SW, Han JK, et al. Randomized prospective trial of the effect of induced hypergastrinemia on the prevention of pancreatic atrophy after pancreatoduodenectomy in humans. Ann Surg. 2003;237:522–9.
40. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Gastroenterol Hepatol (N Y). 2011;7:401–3.
41. Barkin JA, Westermann A, Hoos W, et al. Frequency of appropriate use of pancreatic enzyme replacement therapy and symptomatic response in pancreatic cancer patients. Pancreas. 2019;48:780–6.
42. Gupta A, Muls AC, Lalji A, et al. Outcomes from treating bile acid malabsorption using a multidisciplinary approach. Support Care Cancer. 2015;23:2881–90.
43. Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. Ther Adv Chronic Dis. 2013;4:223–31.
44. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency – breaking the myths. BMC Med. 2017;15:29.

Chapter 44
Chemotherapy for Advanced Pancreatic Cancer: Available Drugs, Mechanisms and Toxicity

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Take Home Messages

- The efficacy of chemotherapy increases with increasing intensity of chemotherapy in both the adjuvant and advanced disease setting; but so does the toxicity
- Treatment selection is dependent on patients' performance status, co-morbidities and aims of therapy
- In advanced disease a significant minority of patients are well enough to receive second-line chemotherapy
- Given the modest efficacy of treatments, patients should be encouraged to participate in clinical trials, where possible

Pearls and Pitfalls

- There are patients who are more likely to respond to platinum agents; particularly those with germ-line BRCA mutations—taking a good family history and considering referral for genetic testing are essential
- An honest discussion with patients about the aims of treatment is important in choosing a regimen (e.g. maximum response from a toxic regimen aimed at shrinkage followed by surgery vs. disease control with less toxicity in the setting of widely metastatic disease)

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- CA19–9 can be a useful biomarker of disease response/progression—but only in the setting of a normal bilirubin
- In patients receiving oxaliplatin, this agent should be reduced or withdrawn before the neuropathy becomes intolerable (as the neuropathy continues to worsen after stopping before improving, if at all)

Future Perspectives

- An increased understanding is needed of selection (or de-selection) biomarkers for chemotherapy agent to ensure that patients likely to benefit most receive specific treatments treatment
- Biomarkers predictive of toxicity are lacking
- The impact of targeting specific actionable somatic mutations within patient's cancer is an active area of investigation
- The impact of the stroma on drug delivery and efficacy needs to be defined and, possibly, targeted
- Harnessing the immune response remains a challenge in pancreatic cancer; rational combinations with systemic therapies warrant investigation

44.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer death in the world, with only 10–20% of patients having resectable disease at presentation. Advanced PDAC, encompassing locally advanced (stage III) and metastatic (stage IV) PDAC, is diagnosed in the majority of people with the disease [1]. Unfortunately even those undergoing a resection have an 85% chance of eventual recurrence, and progressing to an advanced stage [2]. Palliative radiotherapy [3] and chemotherapy are the only therapeutic options available for patients with advanced PDAC, though these result in only modest improvements in survival. The 5-year survival rate for all stages and stage IV disease stands at 9% and 3%, respectively [4].

This chapter will describe the drugs (individually and in combination) and regimens used to treat patients with a focus on advanced PDAC (adjuvant studies are discussed in later in the book), and the pivotal clinical trials (Fig. 44.1) which led to their adoption as standard of care.

44.2 Chemotherapies

44.2.1 Fluoropyrimidines

5-Fluorouracil (5-FU), an antimetabolite chemotherapy in the fluoropyrimidine class, is used to treat many different solid tumours, including breast, cervical, head and neck (H&N) and cancers of the gastrointestinal (GI) tract [5]. 5-FU enters cells via a

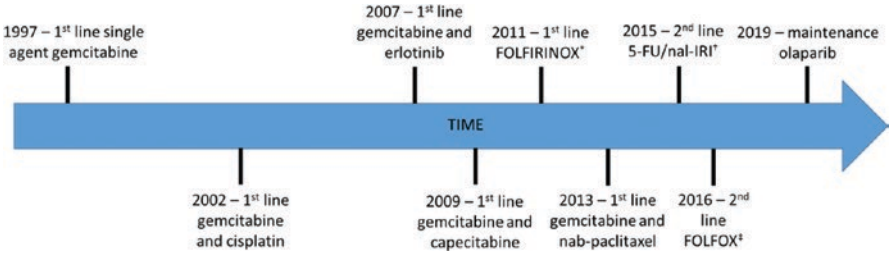

Fig. 44.1 Timeline for the pivotal phase III trials which led to the adoption of the various chemotherapy regimens in the treatment of patients with advanced pancreas cancer. (Asterisk) 5-Fluorouracil, irinotecan, oxaliplatin, and leucovorin. (Dagger) 5-Fluorouracil and liposomal irinotecan. (Double dagger) 5-Fluorouracil, oxaliplatin, and leucovorin

facilitated transport mechanism [6], where it is then converted into several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP). These metabolites inhibit thymidylate synthase (TS), a nucleotide synthetic enzyme essential for normal deoxyribonucleic acid (DNA) replication [7]. TS binds to FdUMP when there is a high intracellular concentration of 5,10-methylenetetrahydrofolate (CH_2THF), a methyl donor. Leucovorin (LV, 5′-formyltetrahydrofolate) is commonly used in combination with 5-FU in clinical practice to increase the intracellular concentration of CH_2THF [5]. FUTP also becomes incorporated into the tumour ribonucleic acid (RNA), inhibiting the survival of the cancer cell line [8]. 5-FU is catabolised in the liver by dihydropyrimidine dehydrogenase (DPD), converting 5-FU to dihydrofluorouracil (DHFU). Inherited DPD deficiency (in <10% of patients) increases the risk of toxicity to 5-FU [9]. Common side effects of 5-FU include myelosuppression, nausea, vomiting diarrhoea and fatigue [10–12].

Capecitabine, an oral pro-drug of 5-FU, avoids DPD mediated catabolism and therefore has improved bioavailability. It is absorbed in the GI tract and is metabolised into 5-FU in the liver and the tumour cells [13, 14]. Capecitabine simulates continuous infusion of 5-FU by exposing the tumour to lower peak concentrations [15]. Side effects are similar to 5-FU, however palmar-plantar erythrodysesthesia (PPE) occurs more commonly with capecitabine [16].

44.2.2 Gemcitabine

Gemcitabine (2′,2′-difluorodeoxycytidine) is an antimetabolite drug (a pyrimidine nucleosides agent), with activity against a variety of solid and haematological malignancies including breast and lung cancer and lymphoma [17, 18]. The main transport mechanism of gemcitabine into the cell is with the human equilibrative nucleoside transporter-1 (hENT-1), a transporter over-expressed in PDAC [19]. Once in the cell, gemcitabine is phosphorylated within the cell into two distinct metabolites: 2′,2′-difluorodeoxycytidine 5′-diphosphate (dFdCDP) and 2′,2′-difluorodeoxycytidine 5′-triphosphate (dFdCTP) which accumulates in the cells and competes with deoxycytidine

triphosphate (dCTP) for incorporation into DNA. This inhibits DNA synthesis, cellular reproduction and progression into the S-phase of the cell cycle [17, 18]. dFdCDP inhibits ribonucleotide reductase, the principal enzyme required for the formation of deoxynucleotide triphosphates for normal DNA synthesis [20]. Gemcitabine toxicity include nausea, vomiting, lethargy, diarrhoea, constipation, myelosuppression, infection, flu-like symptoms and alopecia [18, 21].

44.2.3 Platinum Chemotherapies

Cisplatin, carboplatin and oxaliplatin are platinum-based drugs used to treat various types of solid and haematological malignancies including GI, ovarian, cervical, H&N, non-small-cell lung cancers and lymphomas. The drugs diffuse passively into cells, before undergoing aquation. The aquated forms then bond to purine bases along DNA, forming intra- and inter-strand crosslinks. The intra-strand crosslinks distort the structure of the DNA, interfering with mitosis [22, 23], leading to cancer cell death through apoptosis [24]. Common side effects include myelosuppression, diarrhoea and fatigue. At high doses cisplatin is highly emetogenic, nephrotoxic and can cause hearing loss and tinnitus. Oxaliplatin is commonly associated with peripheral sensory neuropathy [25].

44.2.4 Nab-*Paclitaxel*

Paclitaxel is in the taxane class of chemotherapy drugs [26]. It's main mechanism of action is stabilising microtubules against depolymerisation, essential in mitosis. This in turn prevents the dividing cell from progressing from metaphase into anaphase, leading to eventual apoptosis [27, 28]. Paclitaxel is commonly used for treating ovarian, breast, GI and bladder cancer. The main side effects of paclitaxel are neurotoxicity and myelosuppression, fatigue, diarrhoea, and acute drug reactions [25].

Paclitaxel is poorly-water soluble, and so requires vectors for formulation. Cremophor EL (CrEL-polyethoxylated castor oil) is the usual vector and has been implicated in acute hypersensitivity reactions and neurotoxicity. Despite the use of anti-histamine and corticosteroid pre-medications in paclitaxel containing regimens, 40% and 3% of patients still have minor and life-threatening reactions, respectively [29].

Nanoparticle albumin bound (*nab*-)paclitaxel is an alternate delivery system by which paclitaxel is bound to a molecule of albumin (a natural human carrier responsible for carrying hydrophobic molecules in plasma, such as hormones and vitamins). *Nab*-paclitaxel was developed to enable delivery of higher concentrations of paclitaxel to the tumour with lower toxicity [30]. Higher doses can be infused, with less side effects, with a shorter infusion time, without premedication and with increased anti-tumour activity [28]. *Nab*-paclitaxel is commonly used for treating breast and ovarian cancer.

44.2.5 Irinotecan and Liposomal Irinotecan

Irinotecan is a prodrug that is activated by carboxylesterase enzymes in the liver and colon to the active metabolite, SN-38 [31]. SN-38 is an inhibitor of topoisomerase-I, an enzyme which cleaves the DNA phosphate backbone in order to avoid the natural torsion which occurs as the DNA is changing shape. If not for topoisomerases, this torsion would inhibit DNA and RNA polymerases to function properly, leading to a disruption of replication and transcription [32]. SN-38 is inactivated by the enzyme UDP-glucuronosyltransferase 1-1 [31]. Irinotecan is commonly used alongside 5-FU in colorectal cancer. Common side effects include alopecia, anorexia, cholinergic syndrome and myelosuppression [33, 34].

Liposomal irinotecan (formerly known as nanoliposomal irinotecan or nal-IRI) is irinotecan encapsulated into long-circulating liposome-based nanoparticles. The purpose of its development was to improve the pharmacokinetics and biodistribution of irinotecan, whilst protecting it from premature metabolism [35]. Side effects of nal-IRI include nausea, vomiting, diarrhoea, and fatigue [36].

44.3 Non-chemotherapy Agents

While this chapter is focused on chemotherapy, two additional therapies are included here as they have been directly relevant to the evolution of systemic therapy of PDAC.

44.3.1 Erlotinib

Erlotinib is an oral small molecule which competes with ATP for binding with the intracellular domain of epidermal growth factor receptor HER1/EGFR, thereby inhibiting downstream intracellular signalling [37]. These signals are responsible for cancer-promoting responses such as mitosis, cell motility, cell adhesion, invasion and angiogenesis [38]. Erlotinib is used in EGFR-mutated non-small cell lung cancers [39]. Diarrhoea and acneiform rash are its most common side effects [37].

44.3.2 Olaparib

Olaparib is an oral inhibitor of Poly (ADP-ribose) polymerase (PARP), a group of proteins important for many cellular functions such as DNA repair, apoptosis and genomic stability [40]. PARP inhibitors are commonly used to treat patients with breast and ovarian cancers who have mutations in BReast CAncer (BRCA1 and BRCA2) genes. Germline mutations of BRCA1/2 occur in ~5% of patients with

PDAC [41]. BRCA genes encode for proteins essential for homologous recombination repair of double-strand DNA breaks [42].

PARP inhibitors enable trapping of inactivated PARP at sites of single-strand breaks in cancer cell DNA. The single-strand breaks become irreparable, leading to double-strand breaks. Because the double-strand breaks cannot be repaired either in BRCA1/2 mutant cancers, the DNA damage accumulates and results in tumour cell death [43]. Common side effects of olaparib include fatigue, nausea, vomiting, anaemia, diarrhoea and anorexia [44].

44.4 First Line Palliative Systemic Anti-cancer Regimens

Chemotherapy regimens are usually developed in the advanced disease setting, where it is possible to evaluate their effect in specific malignancies through measurement of radiological response. Having defined a level of activity, drugs and regimens are then tested in the adjuvant setting, where there is no measurable disease to monitor.

The chemotherapy regimens utilised in the treatment of patients PDAC are generally classed as gemcitabine-, 5-FU- or platinum-based according to the nature of the drugs used, or indeed by the number of agents involved as monotherapy, two- and three-drug regimens. The choice of which regimen to offer to patients depends on general fitness to tolerate a multi-drug regimen (judged on Eastern Cooperative Oncology Group or Karnofsky Performance Status (PS)), stage and BRCA1/2 status (Table 44.1). In this section, we summarise how the various common regimens came to be adopted into standard practice.

44.4.1 Gemcitabine

Single-agent 5-FU had been the standard of care palliative chemotherapy for advanced pancreatic cancer until the 1990s [10–12, 45]. The first phase I study investigating gemcitabine in the advanced solid tumour setting [46], was followed in 1994 by a single-arm phase II trial of gemcitabine in advanced PDAC [47]. Forty-five treatment-naïve patients experienced an overall response rate (ORR) of 11% and stable disease (SD) of 31%. Toxicities included neutropenia, thrombocytopenia, flu-like symptoms and an episode of a mild haemolytic-uremic syndrome. A second single arm phase II trial showed a more modest ORR (6.3%) and SD rate (18.8%) [21]. Grade ≥3 adverse events (AEs) were again mainly myelosuppression-related.

Table 44.1 Treatment algorithms for patients with advanced pancreatic cancer based on guidelines by the European Society of Medical Oncology

Baseline characteristics	First line treatment[a]	Second line treatment[a]
ECOG PS 3 or 4 Bilirubin >1.5× ULN Any stage disease Any BRCA1/2 status	Best supportive care.	
ECOG PS 2 Bilirubin >1.5× ULN Any stage disease Any BRCA1/2 status	Single agent gemcitabine	Consider FOLFOX or 5-FU/nal-IRI after disease progression if able to tolerate two-drug regimen Otherwise for best supportive care
ECOG PS 2 Bilirubin <1.5× ULN Stage IV disease BRCA1/2 negative	Gemcitabine and *nab*-paclitaxel	FOLFOX or 5-FU/nal-IRI after disease progression
ECOG PS 2 Bilirubin <1.5× ULN Stage III disease BRCA1/2 negative	Gemcitabine and capecitabine	FOLFOX or 5-FU/nal-IRI after disease progression
ECOG PS 2 Bilirubin <1.5× ULN Any stage disease BRCA1/2-mutated	Gemcitabine and cisplatin	Olaparib maintenance following first-line treatment if licensed and available FOLFOX or 5-FU/nal-IRI after disease progression
ECOG PS 0 or 1 Bilirubin <1.5× ULN Any stage disease Any BRCA1/2 status	FOLFIRINOX	Gemcitabine based chemotherapy after disease progression Olaparib maintenance following first line treatment if BRCA1/2 mutant if licensed and available

[a]Consider clinical trial if available

In the pivotal phase III randomised controlled trial (RCT), published in 1997, 126 patients received either gemcitabine or 5-FU [48]. The primary end point was "Clinical Benefit Response" (CBR), a composite endpoint consisting of improvement or stability of pain score and analgesic use, performance status and weight-change. A CBR was seen in 23.8% of patients with gemcitabine vs. 4.8% with 5-FU ($P = 0.0022$). The 1-year survival rate also favoured gemcitabine (18% vs. 2%, $P = 0.0025$), as did the median progression-free survival (PFS) (9 vs. 4 weeks, $P = 0.0002$) and median overall survival (OS) (5.65 vs. 4.41 months, $P = 0.0025$). Grade ≥3 AEs favoured 5-FU were neutropenia (4.9% vs. 25.9%), thrombocytopenia (1.6% vs. 9.7%), anaemia (9.7% vs. 0%) and nausea/vomiting (12.7% vs. 4.8%). This study showed gemcitabine was well tolerated and resulted in clinical improvement, and therefore it became the first-line treatment for patients with advanced PDAC.

44.4.2 *Gemcitabine and Capecitabine*

Since gemcitabine was established as the first-line therapy for advanced PDAC, investigators have combined it with other drugs in search of more efficacious regimens. The combination of gemcitabine and 5-FU as a continuous infusion had shown promising efficacy [49, 50]. Daily oral capecitabine as an alternative to continuous 5-FU infusion represented an attractive way to avoid the complications arising from indwelling venous catheters. In the first phase I/II trial of gemcitabine and capecitabine in patients with advanced PDAC there was an 18.5% ORR and a 40.7% SD rate, with only 14.3% of patients who received the maximum tolerable dose (MTD) of capecitabine experiencing grade ≥3 AEs [51].

In a randomised phase II study (n = 83), published in 2003, the ORR (17% vs. 14%), SD (56% vs. 43%), median PFS (5.1 vs. 4.0 months) and median OS (9.5 vs. 8.2 months) all favoured the combination arm of gemcitabine and capecitabine compared to single-agent gemcitabine; however, the differences were not significant. Both regimens were well tolerated, with 22% of patients in the gemcitabine arm experiencing grade ≥3 AEs compared to 36% of patients in the combination arm [52]. A smaller single-arm phase II study of gemcitabine and capecitabine observed an ORR of 18.9% and SD of 41.5% in 53 patients; 55% of whom experienced grade ≥3 AEs, mostly related to myelosuppression [53].

Herrmann et al. published the first randomised phase III study in 319 patients with advanced PDAC comparing gemcitabine alone or in combination with capecitabine [54]. The combination arm outperformed monotherapy in both median PFS (4.3 vs. 3.9 months, $P = 0.103$) and median OS (8.4 vs. 7.2 months, $P = 0.234$), neither difference being statistically significant. Grade ≥3 AEs were similar in each arm. Cunningham et al. published a similarly-designed phase III trial in 2009, recruiting 533 patients [15]. The combination arm had superior median OS (7.1 vs. 6.1 months, $P = 0.08$), again not statistically significant. After pooling these results together, a meta-analysis (with additional statistical power) showed the improvement in OS was significant (Hazard ratio [HR] 0.86; 95%-CI, 0.75–0.98; $P = 0.02$). Both treatment arms were well tolerated, with comparable grade ≥3 AEs. At that time, gemcitabine and capecitabine became a standard option for patients with advanced PDAC able to tolerate a two-drug regimen.

44.4.3 *Gemcitabine and* Nab-*Paclitaxel*

In 2011 the first phase I/II study combining *nab*-paclitaxel with gemcitabine in metastatic PDAC reported an ORR 48% and SD 20%; the median PFS was 7.9 months and median OS was 12.2 months [55]. Treatment was generally well tolerated with most AEs being grade 1 or 2.

The MPACT phase III trial, published in 2013, randomised 861 patients with metastatic PDAC to either *nab*-paclitaxel and gemcitabine or single-agent

gemcitabine [56]. Median PFS (5.5 vs. 3.7 months, $P < 0.001$) and median OS (8.5 vs. 6.7 months, $P < 0.001$) all favoured the combination arm. Gemcitabine and *nab*-paclitaxel was well tolerated, but did cause an increased incidence of all grade ≥3 cytopenias, as well as grade ≥3 fatigue, peripheral neuropathy and diarrhoea. This result established this combination as the favoured doublet regimen for fit patients with metastatic PDAC.

44.4.4 Other Lesser-Used Gemcitabine Combinations

Gemcitabine and cisplatin has been extensively studied patients with advanced PDAC [57, 58]. A large phase III trial which reported that although the addition of cisplatin to gemcitabine improved ORR and PFS, it did not significantly improve OS [59]. As there is evidence that the patients with germline BRCA1/2 mutations benefit from platinum-based chemotherapy regimens, cisplatin-gemcitabine may be considered in this subgroup [60].

A gemcitabine-erlotinib combination was investigated in a randomised phase III trial; a total of 569 patients received gemcitabine with either erlotinib or placebo [61]. Median PFS (3.75 vs. 3.55 months, $P = 0.004$) and OS (6.24 vs. 5.91 months, $P = 0.038$) were statistically significantly better in the combination arm. There was some added toxicity (specifically, skin rash) in the erlotinib group. This led to the approval of gemcitabine and erlotinib for advanced PDAC in certain territories, though many did not think that the modest increase in OS was worth the added cost and AEs.

44.4.5 FOLFIRINOX

5-FU, irinotecan, oxaliplatin and leucovorin (FOLFIRINOX) is regarded as the most efficacious but also most toxic chemotherapy regimen used to treat advanced PDAC. A phase I study of FOLFIRINOX in pre-treated patients with solid tumours, in 2003, included six patients with PDAC, one of whom had a complete response (CR) and another a partial response (PR) [62]. The regimen was toxic; 78% of patients needed at least one cycle delay due to toxicity; grade ≥3 AEs included 78% neutropenia, 41% asthenia, 37% peripheral neuropathy.

A phase II study of FOLFIRINOX in treatment-naïve PDAC showed an ORR of 26% (including two patients with CR) with SD in a further 39%; 52% of patients experienced grade ≥ 3 neutropenia, but only 4% of patients had febrile neutropenia. Other grade ≥3 AEs included vomiting (37%), asthenia (22%), and peripheral sensory neuropathy (15%) [63].

Given these encouraging results, a pivotal phase III trial randomised 342 untreated patients with advanced PDAC and an ECOG PS of 0 or 1 to either FOLFIRINOX or single-agent gemcitabine [64]. The median PFS (6.4 vs.

3.3 months, $P < 0.001$), median OS (11.1 vs. 6.8 months, $P < 0.001$) and one year survival (48.4% vs. 20.6%) all favoured FOLFIRINOX. Grade ≥3 neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, and peripheral sensory neuropathy were higher in the FOLFIRINOX arm. The study concluded that FOLFIRINOX should be the preferred first-line option for fit patients with advanced PDAC who could tolerate a three-drug regimen.

44.5 Second Line Palliative Systemic Anti-cancer Regimens

Second-line regimens for patients with disease progression after first-line chemotherapy in the treatment of patients with advanced PDAC will now be discussed.

44.5.1 Oxaliplatin and 5-FU

Oxaliplatin in combination with 5-FU has been a standard of care option for advanced colorectal cancer since the early 2000s [65]. In a phase II study of this combination in patients with advanced PDAC the ORR and SD were 23.3% and 30.0%, respectively. Grade ≥3 AEs included, neutropenia (16%), fatigue (16%), peripheral sensory neuropathy (4.2%) and diarrhoea (14.2%) [66].

In a second phase II study of oxaliplatin, 5-FU and folinic acid (OFF regimen) in 37 patients with advanced PDAC the ORR was 6% and SD was 43%. Grade ≥3 AEs included neuropathy (13.5%), nausea and vomiting (10.8%) and diarrhoea (8.1%) [67]. This regimen was then compared against 5-FU and folinic acid (FF) in 183 patients in the CONKO-003 phase III randomised study [68]. Median PFS (2.9 vs. 2.0 months, $P = 0.019$) and OS (5.9 vs. 3.3 months, $P = 0.010$) both favoured OFF. The incidence of neuropathy was higher in the OFF arm ($P > 0.001$). This study recommended OFF as standard second-line treatment in patients with advanced PDAC following first-line gemcitabine.

However, in 2016, the PANCREOX phase III study randomised 108 patients with advanced gemcitabine-treated PDAC to either 5-FU and leucovorin (FU/LV) or FU/LV plus oxaliplatin (mFOLFOX6) [69]. Median PFS was similar in both arms (3.1 months on mFOLFOX6 vs. 2.9 months on FU/LV, $P = 0.989$). The median OS was however significantly lower with mFOLFOX6 at 6.1 months compared to 9.9 months ($P = 0.024$) in the FU/LV arm. The ≥70 year-old cohort significantly favoured mFOLFOX6 in terms of PFS ($P = 0.015$) and OS ($P = 0.005$) in a subgroup analysis. The authors postulated that younger patients who were randomised to mFOLFOX6 had more adverse prognostic factors compared to their age-matched controls in the FU/LV arm. The incidences of grade ≥3 AEs also favoured FU/LV (11% vs. 63%).

Despite these results, 5-FU, leucovorin and oxaliplatin (FOLFOX) remains a commonly-used second-line option, largely based on the CONKO-003 data.

44.5.2 Liposomal Irinotecan and 5-FU

Irinotecan as monotherapy and in combination has been studied in the second-line setting in patients with advanced PDAC [70, 71]. The first single-arm phase II trial using nal-IRI in gemcitabine pre-treated patients with advanced PDAC was published in 2013 [72]. The 40 patients had an ORR of 7.5% with SD rate of 42.5%. Median PFS and OS were 2.4 months and 5.2 months, respectively; 25% of patients experienced grade ≥3 neutropenia and 20% experienced grade ≥3 fatigue/asthenia.

NAPOLI-1 was a three-arm randomised phase III trial with 417 patients receiving nal-IRI plus 5-FUand folinic acid (5-FU/nal-IRI), nal-IRI monotherapy or FF [36]. The median PFS favoured the combination arm compared to FF (3.1 vs. 1.5 months, $P = 0.0001$) as did median OS (6.1 vs. 4.2 months, $P = 0.012$). Nal-Iri monotherapy achieved a median PFS of 2.7 months and OS of 4.9 months. ORR was 16% in the combination arm, which was significantly higher compared to 1% in the FF arm ($P < 0.0001$). The ORR of nal-IRI was 6%. The nal-IRI arm had the highest incidence of grade ≥3 diarrhoea (21%), vomiting (14%), anorexia (19%), hypokalaemia (12%) as well as death (3%). The combination arm had the highest incidence of grade ≥3 neutropenia (27%) and fatigue (14%). This study led to the adoption of 5-FU/nal-IRI as a standard second-line regimen option in patients with advanced PDAC previously treated with gemcitabine-based regimens.

44.5.3 Maintenance Olaparib

As previously discussed, patients harbouring germline mutations of BRCA1/2 have better outcomes when treated with platinum-containing regimens [60]. Maintenance therapy with PARP inhibitors have been shown to be effective in prolonging PFS in BRCA1/2-mutated ovarian cancers [73]. There is also phase II data to suggest BRCA1/2-mutated patients with advanced PDAC respond to second-line olaparib, with an ORR of 21.7%, and median OS of 9.8 months [44].

The POLO phase III study trial, published in 2019, enrolled 154 patients with germline BRCA1/2-mutated PDAC [74]. Patients must have received ≥16 weeks of platinum-based first-line chemotherapy, resulting in response or SD. Patients were randomised to receive maintenance olaparib or placebo (double-blind). Olaparib maintenance therapy vs. placebo resulted in superior median PFS (7.4 vs. 3.8 months, $P = 0.004$); the median OS is not yet mature (18.9 vs. 18.1 months, $P = 0.68$). ORR was 20% in the olaparib arm vs. 10% in the placebo arm. There was a higher incidence of grade ≥3 fatigue/asthenia (5% vs. 2%) and anaemia (11% vs. 3%) with olaparib. Olaparib may be a maintenance therapy option for patients with BRCA1/2-mutated advanced PDAC after first-line platinum-containing chemotherapy regimens, and highlights the need for molecular profiling in this disease group.

44.6 Conclusion

The prognosis for patients with advanced pancreas cancer is still dismal and novel therapeutic approaches within innovative clinical trial platforms are needed [75]. Collaborative research efforts are required to inform further on the reasons for therapeutic resistance and to identify mechanisms to overcome these obstacles. Many challenges remain in this highly-aggressive malignancy including development of highly-efficacious therapies targeting intracellular pathways as well as the tumour stroma, and learning to harness the immune response.

References

1. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10–27.
2. Lee J, Ahn S, Cho IK, Lee J, Kim J, Hwang J. Management of recurrent pancreatic cancer after surgical resection: systematic review, evidence mapping, and meta-analysis. BMJ. 2018;8(4):1–9.
3. Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013;14(4):317–26.
4. American Cancer Society. Cancer facts & figures. Atlanta, GA: American Cancer Society; 2019. p. 2019.
5. Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330–8.
6. Wohlhueter RM, McIvor RS, Plagemann PG. Facilitated transport of uracil and 5-fluorouracil, and permeation of orotic acid into cultured mammalian cells. J Cell Physiol. 1980;104(3):309–19.
7. Papamichael D. The use of thymidylate synthase inhibitors in the treatment of advanced colorectal cancer: current status. Stem Cells. 2000;18(3):166–75.
8. Kufe DW, Major PP. 5-Fluorouracil incorporation into human breast carcinoma RNA correlates with cytotoxicity. J Biol Chem. 1981;256(19):9802–5.
9. Mattison LK, Fourie J, Desmond RA, Modak A, Saif MW, Diasio RB. Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African-Americans compared with Caucasians. Clin Cancer Res. 2006;12(18):5491–5.
10. Kovach JS, Moertel CG, Schutt AJ, Hahn RG, Reitemeier RJ. Proceedings: a controlled study of combined 1,3-bis-(2-chloroethyl)-1-nitrosourea and 5-fluorouracil therapy for advanced gastric and pancreatic cancer. Cancer. 1974;33(2):563–7.
11. Hansen R, Quebbeman E, Ritch P, Chitambar C, Anderson T. Continuous 5-fluorouracil (5FU) infusion in carcinoma of the pancreas: a phase II study. Am J Med Sci. 1988;295(2):91–3.
12. Tajiri H, Yoshimori M, Okazaki N, Miyaji M. Phase II study of continuous venous infusion of 5-fluorouracil in advanced pancreatic cancer. Oncology. 1991;48(1):18–21.
13. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998;34(8):1274–81.
14. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005;27(1):23–44.
15. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5513–8.

16. Schilsky BRL, Bertucci D, Vogelzang NJ, Kindler HL, Ratain MJ. Dose-escalating study of capecitabine plus gemcitabine combination therapy in patients with advanced cancer. J Clin Oncol. 2002;20(2):582–7.
17. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, et al. Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). Cancer Res. 1990;50(14):4417–22.
18. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
19. Andersson R, Aho U, Nilsson BI, Peters GJ, Pastor-Anglada M, Rasch W, et al. Gemcitabine chemoresistance in pancreatic cancer: molecular mechanisms and potential solutions. Scand J Gastroenterol. 2009;44(7):782–6.
20. Pereira S, Fernandes PA, Ramos MJ. Mechanism for ribonucleotide reductase inactivation by the anticancer drug gemcitabine. J Comput Chem. 2004;30(25):1286–94.
21. Carmichael J, Fink U, Russell RCG, Spittle MF, Harris AL, Spiessi G, et al. Phase II study of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer. 1996;73(1):101–5.
22. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nat Rev Drug Discov. 2005;4(4):307–20.
23. Graham J, Mushin M, Kirkpatrick P. Oxaliplatin. Nat Rev Drug Discov. 2004;3(1):11–2.
24. Pruefer FG, Lizarraga F, Maldonado V, Melendez-Zajgla J. Participation of Omi Htra2 serine-protease activity in the apoptosis induced by cisplatin on SW480 colon cancer cells. J Chemother. 2008;20(3):348–54.
25. NICE. British National Formulary; 2019.
26. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc. 1971;93(9):2325–7.
27. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nat Rev Cancer. 2004;4(4):253–65.
28. Cucinotto I, Fiorillo L, Gualtieri S, Arbitrio M, Ciliberto D, Staropoli N, et al. Nanoparticle albumin bound paclitaxel in the treatment of human cancer: nanodelivery reaches prime-time? J Drug Deliv. 2013;2013:1–10.
29. Sparreboom A, van Zuylen L, Brouwer E, Loos WJ, de Bruijn P, Gelderblom H, et al. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. Cancer Res. 1999;59(7):1454–7.
30. Purcell M, Neault JF, Tajmir-Riahi HA. Interaction of taxol with human serum albumin. Biochim Biophys Acta. 2000;1478(1):61–8.
31. Marsh S, Hoskins JM. Irinotecan pharmacogenomics. Pharmacogenomics. 2010;11(7):1003–10.
32. Champoux JJ. DNA topoisomerases: structure, function, and mechanism. Annu Rev Biochem. 2001;70:369–413.
33. Wagener DJT, Verdonk HER, Dirix LY, Catimel G, Siegenthaler P, Buitenhuis M, et al. Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. Ann Oncol. 1995;6(2):129–32.
34. Ueno H, Okusaka T, Funakoshi A, Ishii H, Yamao K, Ishikawa O, et al. A phase II study of weekly irinotecan as W rst-line therapy for patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2007;59(4):447–54.
35. Drummond DC, Noble CO, Guo Z, Hong K, Park JW, Kirpotin DB. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer Res. 2006;66(6):3271–8.
36. Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan Y-S, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2015;6736(10018):545–57.
37. Hidalgo M, Bloedow D. Pharmacokinetics and pharmacodynamics: maximizing the clinical potential of erlotinib (tarceva). Semin Oncol. 2003;30(3 Suppl 7):25–33.

38. Raymond E, Faivre S, Armand JP. Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. Drugs. 2000;60(Suppl 1):41–2.
39. Wang Y, Schmid-Bindert G, Zhou C. Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. Ther Adv Med Oncol. 2012;4(1):19–29.
40. Herceg Z, Wang ZQ. Functions of poly(ADP-ribose) polymerase (PARP) in DNA repair, genomic integrity and cell death. Mutat Res. 2001;477(1–2):97–110.
41. Holter S, Borgida A, Dodd A, Grant R, Semotiuk K, Hedley D, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015;33(28):3124–9.
42. Walsh CS. Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy. Gynecol Oncol. 2015;137(2):343–50.
43. Connor MJO. Review targeting the DNA damage response in cancer. Mol Cell. 2015;60(4):547–60.
44. Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244–50.
45. Carter SK, Comis RL. The integration of chemotherapy into a combined modality approach for cancer treatment. VI Pancreatic adenocarcinoma. Cancer Treat Rev. 1975;2(3):193–214.
46. Abbruzzese BJL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, et al. A Phase I Clinical, Plasma, and Cellular Pharmacology Study of Gemcitabine. J Clin Oncol. 1991;9(3):491–8.
47. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, et al. Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Investig New Drugs. 1994;12(1):29–34.
48. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
49. Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, et al. Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. J Clin Oncol. 1999;17(2):585–92.
50. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB III. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol. 2002;20(15):3270–5.
51. Hess V, Salzberg M, Borner M, Morant R, Roth AD, Ludwig C, et al. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. J Clin Oncol. 2003;21(1):66–8.
52. Scheithauer W, Schüll B, Schmid K, Raderer M, Haider K, Kwasny W, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. Ann Oncol. 2003;14(1):97–104.
53. Stathopoulos GP, Syrigos K, Polyzos A, Fountzilas G, Rigatos SK, Ziras N, et al. Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. Ann Oncol. 2004;15(2):224–9.
54. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol. 2007;25(16):2212–7.
55. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol. 2011;29(34):4548–54.
56. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.

57. Philip PA, Zalupski MM, Vaitkevicius VK, Arlauskas P, Chaplen R, Heilbrun LK, et al. Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. Cancer. 2001;92(3):569–77.
58. Heinemann V, Wilke H, Mergenthaler HG, Clemens M, König H, Illiger HJ, et al. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. Ann Oncol. 2000;11(11):1399–403.
59. Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. Cancer. 2002;94(4):902–10.
60. Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014;111(6):1132–8.
61. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
62. Ychou M, Conroy T, Seitz JF, Gourgou S, Hua A, Mery-Mignard D, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. Ann Oncol. 2003;14(3):481–9.
63. Conroy T, Paillot B, Franc E, Bugat R, Jacob JH, Stein U, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer—a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol. 2005;23(6):1228–36.
64. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
65. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18(16):2938–47.
66. Tsavaris N, Kosmas C, Skopelitis H, Gouveris P, Kopteridis P, Loukeris D, et al. Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: a phase II study. Investig New Drugs. 2005;23(4):369–75.
67. Pelzer U, Stieler J, Roll L, Hilbig A, Dörken B, Riess H, et al. Second-line therapy in refractory pancreatic cancer. results of a phase II study. Onkologie. 2009;32(3):99–102.
68. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial. J Clin Oncol. 2014;32(23):2423–30.
69. Gill S, Ko Y, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfigar M, et al. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol. 2016;34(32):3914–20.
70. Yi YS, Park YS, Kim HS, Jun JH, Kim HK, Chang HM, et al. Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer. Cancer Chemother Pharmacol. 2009;63(6):1141–5.
71. Gebbia V, Maiello E, Giuliani F, Borsellino N, Arcara C, Colucci G. Irinotecan plus bolus/infusional 5-Fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: a multicenter experience of the Gruppo Oncologico Italia Meridionale. Am J Clin Oncol. 2010;33(5):461–4.
72. Ko AH, Tempero MA, Shan Y-S, Su W-C, Lin Y-L, Dito E, et al. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02 , MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. Br J Cancer. 2013;109(4):920–5.

73. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495–505.
74. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–27.
75. Dreyer SB, Jamieson NB, Cooke SL, Valle JW, Mckay CJ, Biankin AV, et al. PRECISION-Panc: the next generation therapeutic development platform for pancreatic cancer. Clin Oncol (R Coll Radiol). 2020;32:1–4.

Chapter 45
Neoadjuvant Therapy in Upfront Resectable Pancreatic Cancer

Knut Jørgen Labori, Kjetil Søreide, and Svein Dueland

Take Home Messages

- Resectable pancreatic cancer is defined according to the National Comprehensive Cancer Network anatomical classification.
- Upfront surgery followed by adjuvant chemotherapy is the universally accepted standard practice for resectable pancreatic cancer.
- Retrospective studies, meta-analysis and systematic reviews suggest that neoadjuvant chemotherapy is no worse than the traditional upfront surgery approach and may even hold benefit across outcomes.
- Providing modern chemotherapy prior to resection will ensure that almost all patients receive multimodal treatment.
- FOLFIRINOX or gemcitabine with nab-paclitaxel are the preferred neoadjuvant treatment regimens.

Pearls and Pitfalls

- Patients may deteriorate during neoadjuvant chemotherapy, thus preventing subsequent surgery. Some would view this as appropriate clinical selection to avoid high-risk surgical candidates.

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- Patients may progress on neoadjuvant therapy, rendering them locally unresectable or with metastatic disease. Some would argue this in favor of a biological selection to avoid futile surgery.
- Effect of neoadjuvant therapy may be related to the tolerated regimen (e.g. FOLFIRINOX or, modified FOLFIRINOX, or Gemcitabine-based regimen) and number of cycles completed.

Future Perspectives

- There is a call for randomized controlled trials offering direct comparison of neoadjuvant chemotherapy versus upfront surgery followed by adjuvant therapy
- Biomarkers and predictive statistical modeling to identify patients who are more likely to receive and benefit from differing treatment strategies are highly needed
- Ongoing RCTs may change practice towards routine neoadjuvant therapy, given the tolerability and survival benefit is proven to be beneficial
- Future trials and drugs may involve more specific and individualized therapies tailored to the specific tumor type, hopefully with better effect and less toxicity

45.1 Introduction

Historically, patients with pancreatic cancer classified as 'upfront resectable' would, as the nomenclature implies, be taken immediately to surgery. Resectable pancreatic cancer is defined according to the National Comprehensive Cancer Network (NCCN) classification (Box 45.1) as absence of distant organ or lymph node metastases; no tumour contact with the superior mesenteric vein or portal vein, or ≤180° contact with either vein without vein contour irregularity, and no tumor contact with (i.e. existence of clear fat planes around) the coeliac axis, common hepatic, and superior mesenteric artery [1]. With novel chemotherapy regimens, the concept of 'resectability' has changed, hence the previous definitions and terminology may become mixed or confused. Borderline and locally advanced disease is discussed in separate chapters of this book.

Box 45.1 National Comprehensive Cancer Network Definition of Resectable Pancreatic Cancer [1]

Arterial	No arterial tumour contact	Celiac axis Superior mesenteric artery Common hepatic artery
Venous	No tumour contact or tumour contact ≤180° without vein contour irregularity	Portal vein Superior mesenteric vein
	No distant metastases	

Currently, upfront surgery is the universally accepted standard practice for resectable pancreatic cancer (Fig. 45.1). However, even after curative surgery, the oncological results of surgery alone are disappointing—the majority of patient eventually recur and a considerable proportion experience early dissemination of disease, despite attempt at radical surgery for cure. Therefore, surgery is integrated into a complete multimodal treatment sequence including surgery and adjuvant chemotherapy. Several observations have led to a gradual change in concept regarding chemotherapy, namely, to apply neoadjuvant chemotherapy before surgery in an increasing number of patients. In the current chapter we will discuss the specific setting of entertaining the concept of neoadjuvant chemotherapy to patients with otherwise resectable pancreatic cancer.

45.2 Progress in Adjuvant Treatment

Notable progress has been observed with the use of adjuvant chemotherapy during the last 15 years. ESPAC-1 and CONKO-001 demonstrated that adjuvant chemotherapy with either 5-fluorouracil plus folinic acid or gemcitabine significantly improved overall and 5-year survival compared with surgery alone [2–4]. Further progress was made with ESPAC-4 demonstrating a survival benefit of combination therapy with gemcitabine and capecetabine versus gemcitabine monotherapy [5]. Finally, PRODIGE has shown a significant survival benefit of fluorouracil, folinic acid, irinotecan, and oxaliplatin (mFOLFIRINOX) versus gemcitabine (overall survival 54.4 vs. 35 months; $P = 0.003$) [6].

All patients with resected pancreatic cancer who do not receive neoadjuvant therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications (Fig. 45.1). mFOLFIRINOX is now the preferred adjuvant regimen in fit patients in current international guidelines from NCCN, European Society for Medical Oncology, and American Society of Clinical Oncology (ASCO) [1, 7, 8]. Alternatively, doublet therapy with gemcitabine and capecitabine or monotherapy with gemcitabine or 5-fluorouracil plus leucovorin can be offered.

Of note, patients recruited into trials on adjuvant chemotherapy after pancreatectomy have been carefully assessed before receiving chemotherapy. Details on screening failures and reasons for exclusion are usually not reported. The discrepancy of trial compliance (some report >80% completion of adjuvant therapy after surgery) to real-life settings (compliance reported in 40–65% or less) is of concern, as the general impression is that many patients do not receive or, are not fit for adjuvant chemotherapy after what may have been a complex post-operative course. Detection of metastatic disease intraoperatively, development of overt metastases during their postoperative recovery period, and inability to recover functionally or nutritionally to be able to start adjuvant therapy in a timely manner make several patients not candidates for these trials [9].

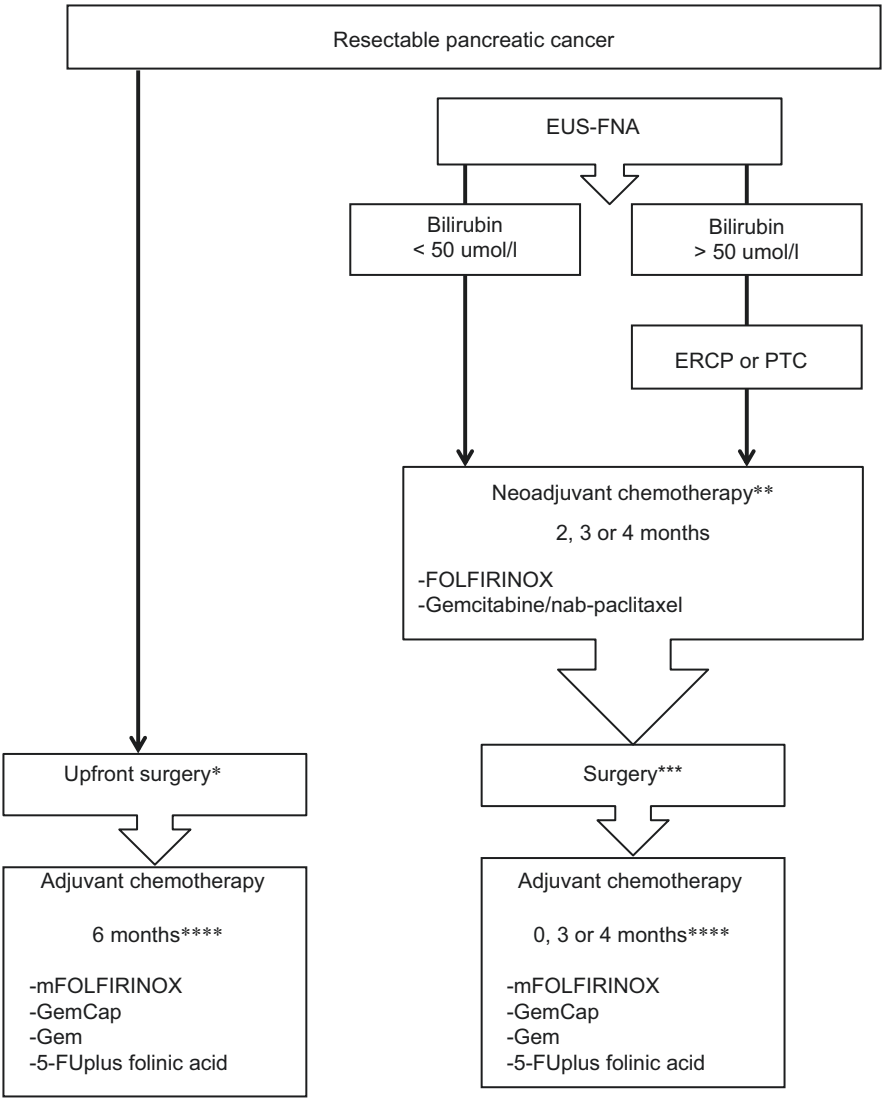

Fig. 45.1 Diagnostic workup and treatment recommendations in patients undergoing neoadjuvant chemotherapy or upfront surgery for resectable pancreatic cancer [22]. (*) Supported by data from randomized controlled trials. (**) Clinical protocol preferred. Duration of neoadjuvant chemotherapy in ongoing trials: 2, 3 or 4 months [29, 30, 32]. (***) Surgery scheduled 4 weeks after last course of chemotherapy. (****) Overall 6 months of chemotherapy in both treatment sequences. Duration of adjuvant chemotherapy: 6 months after upfront surgery. Duration of adjuvant chemotherapy in ongoing trials: 0, 3 or 4 months. *ERCP* endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS-FNA* endocopic ultrasound—fine needle aspiration, *(m)FOLFIRINOX* (modified) fluorouracil, folinic acid, irinotecan, and oxaliplatin, *GemCap* gemcitabine and capecitabine, *5-FU* fluorouracil

45.3 Neoadjuvant Approach

The neoadjuvant approach has become the standard of care for several gastrointestinal cancers, including patients with gastric, esophageal and selected rectal cancers and patients with colorectal liver metastases [10–12]. The lack of efficient chemotherapy regimens has hampered the use of neoadjuvant therapy in resectable pancreatic cancer. FOLFIRINOX and gemcitabine/nab-paclitaxel have improved survival in metastatic pancreatic cancer [13, 14]. Moreover, the use of these regimens as neoadjuvant therapy in locally advanced pancreatic cancer is promising [15]. In addition, given the significant survival benefit of adjuvant mFOLFIRINOX in resectable pancreatic cancer, proponents of the neoadjuvant approach suggest that neoadjuvant therapy could be preferred also in patients with resectable pancreatic cancer [6]. To date there are no prospective data proving an advantage of neoadjuvant therapy over upfront surgery for resectable pancreatic cancer. However, the rationale for a neoadjuvant approach in pancreatic cancer may be particularly strong. Pancreatic cancer has been shown to be systemic from the earliest stages and thus an early systemic approach may be essential in the attempt to achieve cure [16]. Indeed, about 15% of patients who undergo upfront surgery develop distant spread only a few months postoperatively, indicating that subclinical distant metastasis is likely to have been present already at diagnosis [17].

Moreover, the cancer operation is often complex and associated with a relatively high morbidity. Therefore, it is of great importance to biologically select only those patients who are most likely to benefit from surgery [9].

45.4 Current Evidence for a Neoadjuvant Approach

Current evidence of an effect of neoadjuvant therapy on long-term outcomes comes mainly from phase II trials and retrospective analyses. In addition, several systematic reviews and metaanalyses on the topic have been performed [18–23]. These studies conclude that neoadjuvant chemotherapy for treatment of resectable pancreatic cancer is no worse than traditional upfront surgery approach and may even hold benefit across outcomes. However, there is a call for randomized controlled trials offering direct comparison of neoadjuvant chemotherapy versus upfront surgery followed by adjuvant therapy. Indeed, several ongoing clinical trials are currently investigating neoadjuvant treatment in upfront resectable pancreatic cancer [20, 24].

45.4.1 Observational Studies

A retrospective study covering 25 years of the MD Anderson' Cancer Center experience of neoadjuvant therapy for pancreatic cancer with chemotherapy and/or chemoradiation reported a progressive improvement of median overall survival from 24–28 to

37–42 months despite more complex operations with an increase in vascular resections [25]. A metanalysis of 38 studies with 3484 patients comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer, of whom 1738 (49.9%) had neoadjuvant treatment, showed that overall survival by intention to treat was significantly better for neoadjuvant treatment compared to upfront surgery (18.8 vs. 14.8 months) [18]. The difference in overall survival was larger among patients whose tumours were resected (26.1 vs. 15.0 months). Notably, most of the data from these studies are from retrospective series or, at best, prospective cohorts.

45.4.2 Randomized Trials

Only three randomized controlled trials comparing upfront surgery with neoadjuvant chemotherapy in resectable pancreatic cancer have been completed, as of the time of writing [26–28], the PACT-15 trial, the PREOPANC-1 trial and the Prep-02/JSAP-05 trial.

The PACT-15 trial randomized 93 patients (in a 1:1:1 design) to receive surgery followed by six cycles of adjuvant gemcitabine (arm A), surgery followed by six cycles of adjuvant PEXG (cisplatin, epirubicin, and gemcitabine) (arm B), or three cycles of PEXG before and three cycles after surgery (arm C, neoadjuvant arm) [26]. Primary endpoint was event-free at 1 year (event-free defined as freedom from progression, relapse, new tumour occurrence, distant metastases, or death). In the per-protocol population, 23% (n = 6) of the patients in group A, 50% (n = 15) in group B, and 66% (n = 19) in group C were event-free at 1 year. Median overall survival was 20.4 months in the surgery plus gemcitabine group, 26.4 months in the surgery plus adjuvant PEXG group, and 38.2 month in the neoadjuvant PEXG strategy. Intention-to-treat estimates of 5-year overall survival were 13%, 24%, and 49% in the three arms, respectively. Of note, since the trial began, the standard of care for adjuvant therapy altered, and other chemotherapy regimens have developed. Thus, the authors decided to not continue with the phase 3 part of the PACT-15. However, one may in part use the outcome of this trial as a "proof of principle" in terms of the benefit of a neoadjuvant approach (compared to adjuvant only), although comparison to more effective chemo-regimens is not possible.

In the PREOPANC-1 trial 248 patients with resectable or borderline resectable pancreatic cancer were randomly assigned to preoperative gemcitabine-based chemoradiotherapy (preceded and followed by a modified course of gemcitabine) followed by three cycles after surgery or upfront surgery followed by six cycles of adjuvant gemcitabine [27]. Preliminary results showed that in an intent-to-treat analysis, the resection rate was slightly lower with neoadjuvant chemoradiotherapy than with upfront surgery (60% vs. 72%; P = 0.065) but the R0 resection rate was significantly increased (61% vs. 31%; $P < 0.001$). Moreover, the median time until recurrence was significantly longer after neoadjuvant treatment (9.9 vs. 7.9 months; P = 0.023). The median overall survival was 17.1 months after preoperative chemoradiotherapy compared with 13.7 months after upfront surgery followed by adjuvant chemotherapy (P = 0.074). Longer follow up and final survival results are

needed before any definitive conclusion. Of note in the following PREOPANC-2 trial patients with resectable and borderline resectable pancreatic cancer are randomized to receive either neoadjuvant 8 courses FOLFIRINOX followed by surgery (no adjuvant) or neoadjuvant gemcitabine based chemoradiotherapy followed by surgery and adjuvant gemcitabine.

In the Prep-02/JSAP-05 trial 364 patients with resectable pancreatic cancer were randomly assigned to receive neoadjuvant chemotherapy using two courses gemcitabine and S1 followed by surgery and adjuvant S1 with upfront surgery and adjuvant S1 [28]. The median overall survival was 36.7 months after neoadjuvant treatment and 26.6 months after upfront surgery ($P = 0.015$).

45.4.3 Current Controversy and Debate

Uncertainty related to the existing body of research of the neoadjuvant approach has led critics to highlight the limitations of drawing too optimistic conclusions from small studies that are underpowered and caution against loosing the window of resectability [21]. More efficient first-line regimens, such as FOLFIRINOX and gemcitabine with nab-paclitaxel have improved overall survival in fit patients with metastatic disease and, may lead to conversion to surgery in some patients with locally advanced pancreatic cancer previously deemed unresectable.

Of note, ASCO currently recommends neoadjuvant therapy for patients with anatomically resectable tumors, but with radiographic findings suspicious but not diagnostic for extrapancreatic disease, a performance status or comorbidity profile not currently appropriate (but potentially reversible) for a major abdominal operation or a CA 19-9 level (in absence of jaundice) suggestive of disseminated disease [7].

Thus, neoadjuvant chemotherapy seems to represent a reasonable alternative to upfront surgery for patients with resectable pancreatic cancer, but such patients should ideally be treated as part of a clinical protocol. The main ongoing randomized phase III trials of neoadjuvant chemotherapy for resectable pancreatic cancer now use FOLFIRINOX or gemcitabine with nab-paclitaxel as treatment regimens [24, 29, 30]. The duration of neoadjuvant chemotherapy in these trials differ from 2 to 4 months before surgery (Fig. 45.1) [29, 31, 32]. Surgery is scheduled 4 weeks after the last course of chemotherapy.

45.5 Potential Advantages with a Neoadjuvant Approach

45.5.1 Compliance to Chemotherapy

Postoperative morbidity and even mortality after pancreatic surgery, can preclude adjuvant therapeutic delivery. Complications following pancreatectomy affect about 60% of the patients [33–35]. The technical complexity of the operation and the

often frail and co-morbid patient population contribute to the high complication rate. Several studies have confirmed that only 50–70% of patients undergoing upfront surgery initiate adjuvant chemotherapy, whereas very few studies report the completion rate of adjuvant chemotherapy [18, 36–39]. In addition to higher age, worse performance status, and early disease recurrence, the causes of not receiving adjuvant chemotherapy is mostly related to surgical complications, especially post-operative pancreatic fistula and post-pancreatectomy hemorrhage [36, 37, 39].

Considering the significant survival benefit of adjuvant chemotherapy, the initiation and completion rates reported in the literature remain relatively low (<50%). Providing modern chemotherapy prior to resection will ensure that almost all patients receive this modality. Successful implementation of neoadjuvant therapy should thus increase the rate of patients having both treatment modalities (Box 45.2).

Box 45.2 Potential Advantages and Disadvantages with Neoadjuvant Chemotherapy in Resectable Pancreatic Cancer

Advantages

- Ensure that all patients receive chemotherapy
- Treat micrometastatic disease earlier, at the time of diagnosis
- Decrease surgical complexity
- Allow emergence of resistant, occult (subclinical) metastatic disease
- Avoid futile surgery (in non-curable disease)
- Give patients time to improve their performance and cardiopulmonary status before major surgery
- Improve histopathological parameters (R0 resection rate and pathological lymph node rate) by reducing tumour bulk and involvement of nearby structures

Disadvantages

- Complications related to associated use of invasive procedures (ERCP or PTC, EUS-FNA)
- Low rate of complete or clinically relevant pathologic or radiological response
- Systemic toxicity to chemotherapy
- Progression during neoadjuvant chemotherapy

ERCP endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS-FNA* endocopic ultrasound—fine needle aspiration

45.5.2 Managing Micrometastatic Disease

Both preclinical and clinical data support the contention that even early-stage pancreatic cancer is a systemic disease. A large single centre study on 692 patients undergoing pancreatectomy for pancreatic cancer found that 76% of recurrences occur at a distant site, indicating that most patients with pancreatic cancer have

systemic disease at the time of resection [17]. Additionally, almost 20% of the patients who were free of recurrence after 5 years went on to develop disease recurrence.

45.5.3 Test of Biology: Allow Emergence of Occult Metastatic Disease

Up to 15–20% of patients with resectable pancreatic cancer who undergo surgical resection upfront have early manifestation of metastasis [17, 36]. Several studies report that early disease recurrence is a major cause of not initiating or not completing adjuvant chemotherapy [3, 36, 39]. Even in well designed randomized controlled trials on adjuvant chemotherapy with good performance status patients and strict tumour biology inclusion criteria such as low CA 19-9 levels, early disease recurrence is an important cause of discontinuation of adjuvant therapy. Thus, probably up to 15% of patients with resectable pancreatic cancer receiving neoadjuvant therapy may fail to undergo subsequent resection due to early manifestation of metastases, inability to optimize performance status or comorbidities during neoadjuvant therapy [3, 5, 40]. Patients with rapidly progressive disease under neoadjuvant therapy can be spared major surgery, which is unlikely to be beneficial and associated with significant morbidity.

45.5.4 Test of Performance Status Before Major Surgery

Poor functional capacity and malnutrition may increase the rate of surgical complications.

At time of diagnosis several patients with pancreatic cancer suffer from weight loss and symptoms related to biliary obstruction or pancreatic endocrine or exocrine insufficiency. Relive of biliary obstruction and treatment of endocrine or exocrine insufficiency would improve the patients performance and nutritional status. Although these patients may not be candidates for systemic chemotherapy, current guidelines recommend to consider neoadjuvant chemotherapy in patients with a performance status or comorbidity profile not currently appropriate, but potentially reversible for a major abdominal operation [7].

Prehabilitation programs aim to optimise and improve functional capacity before surgery in order to reduce the risk of postoperative recovery. The beneficial effect of such protocols is not well established, and the precise protocol of prehabilitation has not been completely established. However, prehabilitation before major abdominal surgery has shown to reduce overall and pulmonary morbidity [41]. Cardiopulmonary exercise training concurrent with neoadjuvant chemotherapy and/or chemoradiation for pancreatic cancer has shown to increase physical activity [42].

45.5.5 Decrease Surgical Complexity

Patients treated with neoadjuvant therapy do not experience more complications from surgery than patients undergoing upfront surgery [43–45]. However, definite conclusions cannot be drawn, as most observations come from small studies, including heterogeneous neoadjuvant regimens and without comparison with upfront surgery groups. A study comparing 346 patients receiving neoadjuvant therapy with 407 patients undergoing upfront surgery for borderline resectable or locally advanced pancreatic cancer showed that the rate of clinically relevant postoperative pancreatic fistula was 3.6-fold lower in patients receiving neoadjuvant therapy versus upfront resection (3.8% vs. 13.8%; $P < 0.001$) [45]. In addition, factors associated with postoperative pancreatic fistula changed after neoadjuvant therapy, and only soft pancreatic texture was associated with a higher risk of postoperative pancreatic fistula (38.5% vs. 6.3%; $P < 0.001$).

45.5.6 Improve Resection Margin and Lymph Node Status

The resection margin status (R0/R1) and pathological lymph node rate among patients actually undergoing tumour resection has been shown to be significantly better in patients undergoing neoadjuvant therapy [18, 26, 27, 46]. The lower pathological lymph node rate in patients undergoing neoadjuvant therapy may be the result of the neoadjuvant treatment causing regression of lymph node metastases. A definition of microscopic margin involvement (R1) appropriate for pancreatic cancer following neoadjuvant therapy is lacking [47]. Margin assessment based on 0 mm or 1 mm minimum clearance, as currently used for upfront resected pancreatic cancer, is likely to underestimate R1 resection in the neoadjuvant setting. Thus, whether the R0 rate after neoadjvant therapy really decrease is under debate [47].

Most studies describing pathological changes in the pancreas concerns neoadjuvant chemoradiotherapy [47]. Chemoradiation can affect the morphological appearance of both the tumour and non-neoplastic pancreatic parenchyma, i.e. more pancreatic and stromal fibrosis, hypertrophic nerves and islet cell aggregation, but less inflammation in the non-neoplastic pancreas [48, 49]. In most cases, fibrosis is the dominant feature of tumour regression in case of good response to treatment. In addition to inducing fibrosis preoperative chemoradiation to well-oxygenated tissues with intact blood supply may enhance the effectiveness of drug delivery and reduce hypoxia-related resistance to chemoradiation and radiation-related toxicity [42].

45.6 Potential Disadvantages with a Neoadjuvant Approach

45.6.1 Complications Related to Invasive Procedures

Statistically, some primary resectable patients undergoing neoadjuvant treatment will experience severe complications related to the invasive treatment of jaundice via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) or correlated to endoscopic ultrasound (EUS) needed to obtain cytological or histological specimen before medical treatment (Fig. 45.1). In patients undergoing upfront surgery biopsy proof is not required before proceeding with resection [50]. A systematic review of 10,941 EUS procedures (including 51 studies) with fine needle aspiration indicates overall complication risk of 0.98% (107 patients) (acute pancreatitis $n = 36$ patients; mild in 33, severe in 3), bleeding in 14 patients, chest or abdominal pain ($n = 37$), fever ($n = 12$), infection ($n = 5$), perforation ($n = 2$), and bile leak in one patient [51–53]. Mortality was reported in two patients (0.02%). The risk of acute pancreatitis in the general study was 0.44% (36 of 8246) with mild in 0.40% and severe in 0.036%. Greater complication risk is assumed in endoscopic fine needle puncture of pancreatic cysts than in solid pancreatic tumors and in patients in poor general condition and/or with comorbidity.

There has been a controversy between the benefits and adverse effects of preoperative biliary drainage before pancreatic resection [54]. A randomized controlled trial comparing a strategy of endoscopic preoperative biliary drainage followed by surgery, with a strategy of early surgery showed significantly more serious complications in patients who underwent preoperative biliary drainage compared with those who went for early surgery (74% vs. 39%; $P < 0.001$) [55]. The difference in overall complication rate was largely due to a high rate of complications owing to preoperative biliary drainage. However, mortality, length of hospital stay and long term survival did not differ significantly between the two groups. The clinical practice at the time of the trial was to use plastic stents, and a later study showed that fully covered self-expandable metal stents yield a better outcome than plastic stents in case of preoperative biliary stenting [56]. Thus, although early surgery without preoperative biliary drainage remains the treatment of choice, fully covered self-expandable metal stents should be preferred over plastic stents whenever preoperative biliary drainage is indicated [56].

ERCP related complications include post ERCP pancreatitis, bleeding, infections (cholangitis, cholecystitis), perforation (duodenal, periampullary), and cardiopulmonary [57]. The overall incidence of post ERCP pancreatitis is estimated to be 3% to 10% in systematic reviews, with a majority of cases being mild, and an overall mortality rate of 0.7% [57]. Large studies have identified numerous patient-related, procedure-related, and operator-related factors that have been associated with post ERCP pancreatitis.

Of note, studies on preoperative biliary drainage in the course of an upfront or neoadjuvant approach in resectable pancreatic cancer do not report the derailment from a surgical pathway by stent related complications, but focus on the rates of stent related complications and their postoperative sequelae [55, 56, 58, 59].

45.6.2 Low Rate of Complete or Significant Radiological or Pathologic Response

A systematic review on 14 studies involving 365 patients with locally advanced pancreatic cancer found a complete pathologic response in 6 of 85 (7%) resected specimens, and a total RECIST response rate of 29% [15]. A large singe center study on an unselected cohort of 680 prospectively enrolled patients with borderline and locally advanced pancreatic cancer analyzed the RECIST response in 408 patients completing the planned chemotherapy cycles: 125 patients (30.6%) had a partial response, 128 (31.4%) had a stable disease, and 155 (38.0%) had a disease progression [60]. A study of 583 patients undergoing neoadjuvant therapy with chemotherapy or chemoradiotherapy showed a major pathologic response in 77 patients (13.2%) including 23 (3.9%) who had a complete pathologic response [61]. Thus, a complete pathological response of 3.9–7% and a radiological response of about 30% of the patients may be expected during neoadjuvant chemotherapy.

45.6.3 Therapeutic Toxicity

A systematic review and patient-level meta-analysis on neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer showed that neutropenia, diarrhea, and fatigue were the most commonly reported grade III–IV adverse events [62]. No deaths were attributed to FOLFIRINOX. In PRODIGE-1, no deaths occurred in patients receiving mFOLFIRINOX adjuvant, and all the toxic effects were reversible, except for oxaliplatin-induced peripheral neurotoxic effect, which was persistent at 3 years in two patients in the modified-FOLFIRINOX group [6]. In a randomized clinical trial on FOLFIRINOX as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic treatment-related grade 3 or 4 adverse events occurred in 5% of the patients, and one patient died from febrile neutropenia [13].

45.6.4 Progression During Neoadjuvant Therapy

The resection rate in patients undergoing a neoadjuvant or upfront surgery approach has been difficult to establish as most retrospective studies do not have an intention to treat design. A metaanalysis of studies with an intention to treat design showed

lower resection rate with a neoadjuvant approach (66% vs. 81.3%; $P < 0.001$). However, the PREOPANC-1, PACT, and Prep-02/JSAP-05 trials did not show a significant difference in the resection rate between the neoadjuvant and upfront surgery approach (PREOPANC-1: 62% vs. 72%; $P = 0.15$, PACT: 87.5% in both arms) [26–28]. The risk for local progression during neoadjuvant therapy is probably low, and a rate of 1.4–3.1% has been reported [26, 40]. The risk of development of distant metastases during neoadjuvant therapy has been reported to be up to 15% [26, 40]. Of note this rate equals the occurrence of early distant metastases within 3–4 months after upfront surgery [17, 36]. While local progression during neoadjuvant therapy is a major concern, patients with early distant metastases after major pancreatectomy probably have undergone the stress of pancreatectomy for no oncologic gain. However, the risk for disease progression and losing a curative surgical window highlights the need for appropriate patient identification and additional prospective comparative studies. Biomarkers to aid in the preoperative clinical decision-making are still lacking. Hence, exploring biomarkers and predictive statistical modeling to identify patients who are more likely to receive and benefit from differing treatment modalities within competing pathways are highly needed.

45.7 Conclusions

Current evidence of an effect of neoadjuvant chemotherapy on long-term outcomes comes mainly from phase II trials and retrospective analyses. Neoadjuvant chemotherapy for treatment of resectable pancreatic cancer is no worse than traditional upfront surgery approach and may even hold clinical benefits. However, it may result in the risk of losing an opportunity for surgery. Large volume, well-designed randomized controlled trials are warranted to evaluate the potential advantages and disadvantages and gain of overall survival in patients with resectable pancreatic cancer who receive neoadjuvant chemotherapy before surgery.

References

1. NCCN. Practice guidelines in oncology: pancreatic adenocarcinoma v3.2019.
2. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200–10.
3. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297:267–77.
4. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304:1073–81.
5. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389:1011–24.

6. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395–406.
7. Khorana AA, McKernin SE, Berlin J, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. J Clin Oncol. 2019;37:2082–8.
8. Committee EG. eUpdate: cancer of the pancreas treatment recommendations; 2019. https://www.esmoorg/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Cancer-of-the-Pancreas-Treatment-Recommendations.
9. Ko AH. Shifting the treatment model for resectable pancreatic cancer. Lancet Gastroenterol Hepatol. 2018;3:375–6.
10. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v38–49.
11. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v50–v7.
12. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol. 2018;29:44–70.
13. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
14. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
15. Rombouts SJ, Walma MS, Vogel JA, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol. 2016;23:4352–60.
16. Sohal DP, Walsh RM, Ramanathan RK, Khorana AA. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. J Natl Cancer Inst. 2014;106:dju011.
17. Groot VP, Rezaee N, Wu W, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. Ann Surg. 2018;267:936–45.
18. Versteijne E, Vogel JA, Besselink MG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105:946–58.
19. Dhir M, Malhotra GK, Sohal DPS, et al. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. World J Surg Oncol. 2017;15:183.
20. Blair AB, Sorber R, Rozich NS, Burkhart RA. A qualitative review of neoadjuvant chemotherapy in resectable pancreatic adenocarcinoma. Pancreas. 2019;48:973–84.
21. Bradley A, Van Der Meer R. Upfront surgery versus neoadjuvant therapy for resectable pancreatic cancer: systematic review and Bayesian network meta-analysis. Sci Rep. 2019;9:4354.
22. Araujo RLC, Silva RO, de Padua SC, et al. Does neoadjuvant therapy for pancreatic head adenocarcinoma increase postoperative morbidity? A systematic review of the literature with meta-analysis. J Surg Oncol. 2020;121(5):881–92.
23. Ye M, Zhang Q, Chen Y, et al. Neoadjuvant chemotherapy for primary resectable pancreatic cancer: a systematic review and meta-analysis. HPB (Oxford). 2020;22(6):821–83.
24. Lambert A, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol. 2019;11:1758835919875568.
25. Cloyd JM, Katz MH, Prakash L, et al. Preoperative therapy and pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a 25-year single-institution experience. J Gastrointest Surg. 2017;21:164–74.
26. Reni M, Balzano G, Zanon S, et al. Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2-3 trial. Lancet Gastroenterol Hepatol. 2018;3:413–23.
27. Tienhoven GV, Versteijne E, Suker M, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): a randomized, controlled, multicenter phase III trial. J Clin Oncol. 2018;36:LBA4002-LBA.

28. Unno M, Motoi F, Matsuyama Y, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05). J Clin Oncol. 2019;37:189.
29. Labori KJ, Lassen K, Hoem D, et al. Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) - study protocol for a national multicentre randomized controlled trial. BMC Surg. 2017;17:94.
30. Sohal D, McDonough SL, Ahmad SA, et al. SWOG S1505: a randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinom. J Clin Oncol. 2017;35:TPS508-TPS.
31. Sohal D, McDonough S, Ahmad SA, et al. SWOG S1505: initial findings on eligibility and neoadjuvant chemotherapy experience with mfolfirinox versus gemcitabine/nab-paclitaxel for resectable pancreatic adenocarcinoma. J Clin Oncol. 2019;37:414.
32. Dutch Pancreatic Cancer Group. The (cost)effectiveness of neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine based chemoradiotherapy and adjuvant gemctiabine for (borderline) resectable pancreatic cancer – PREOPANC-2 study. 2019. http://www.dpcgnl/projecten/preopanc-2html.
33. Ziegler KM, Nakeeb A, Pitt HA, et al. Pancreatic surgery: evolution at a high-volume center. Surgery. 2010;148:702–9.
34. DeOliveira ML, Winter JM, Schafer M, et al. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006;244:931–7.
35. Sanchez-Velazquez P, Muller X, Malleo G, et al. Benchmarks in pancreatic surgery: a novel tool for unbiased outcome comparisons. Ann Surg. 2019;270:211–8.
36. Labori KJ, Katz MH, Tzeng CW, et al. Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma – a population-based cohort study. Acta Oncol. 2016;55:265–77.
37. Mackay TM, Smits FJ, Roos D, et al. The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis. HPB (Oxford). 2019;22(2):233–40.
38. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg. 2014;260:372–7.
39. Tzeng CW, Tran Cao HS, Lee JE, et al. Treatment sequencing for resectable pancreatic cancer: influence of early metastases and surgical complications on multimodality therapy completion and survival. J Gastrointest Surg. 2014;18:16–25.
40. Tzeng CW, Fleming JB, Lee JE, et al. Defined clinical classifications are associated with outcome of patients with anatomically resectable pancreatic adenocarcinoma treated with neoadjuvant therapy. Ann Surg Oncol. 2012;19:2045–53.
41. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. World J Surg. 2019;43:1661–8.
42. Ngo-Huang A, Parker NH, Wang X, et al. Home-based exercise during preoperative therapy for pancreatic cancer. Langenbecks Arch Surg. 2017;402:1175–85.
43. Marchegiani G, Andrianello S, Nessi C, et al. Neoadjuvant therapy versus upfront resection for pancreatic cancer: the actual spectrum and clinical burden of postoperative complications. Ann Surg Oncol. 2018;25:626–37.
44. Cooper AB, Parmar AD, Riall TS, et al. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? J Gastrointest Surg. 2015;19:80–6; discussion 6–7.
45. Hank T, Sandini M, Ferrone CR, et al. Association between pancreatic fistula and long-term survival in the era of neoadjuvant chemotherapy. JAMA Surg. 2019;154(10):943–51.
46. Schorn S, Demir IE, Reyes CM, et al. The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma – a systematic review and meta-analysis. Cancer Treat Rev. 2017;55:96–106.

47. Verbeke C, Lohr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev. 2015;41:17–26.
48. Chatterjee D, Katz MH, Rashid A, et al. Pancreatic intraepithelial neoplasia and histological changes in non-neoplastic pancreas associated with neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma. Histopathology. 2013;63:841–51.
49. Kalimuthu SN, Serra S, Dhani N, Chetty R. The spectrum of histopathological changes encountered in pancreatectomy specimens after neoadjuvant chemoradiation, including subtle and less-well-recognised changes. J Clin Pathol. 2016;69:463–71.
50. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155:887–92.
51. Wang KX, Ben QW, Jin ZD, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointest Endosc. 2011;73:283–90.
52. Carrara S, Arcidiacono PG, Mezzi G, Petrone MC, Boemo C, Testoni PA. Pancreatic endoscopic ultrasound-guided fine needle aspiration: complication rate and clinical course in a single centre. Dig Liver Dis. 2010;42:520–3.
53. Hamada T, Yasunaga H, Nakai Y, et al. Severe bleeding and perforation are rare complications of endoscopic ultrasound-guided fine needle aspiration for pancreatic masses: an analysis of 3,090 patients from 212 hospitals. Gut Liver. 2014;8:215–8.
54. Mumtaz K, Hamid S, Jafri W. Endoscopic retrograde cholangiopancreaticography with or without stenting in patients with pancreaticobiliary malignancy, prior to surgery. Cochrane Database Syst Rev. 2007;2007(3):CD006001.
55. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362:129–37.
56. Tol JA, van Hooft JE, Timmer R, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2016;65:1981–7.
57. Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017;85:32–47.
58. Kim BJ, Prakash L, Narula N, et al. Contemporary analysis of complications associated with biliary stents during neoadjuvant therapy for pancreatic adenocarcinoma. HPB (Oxford). 2019;21:662–8.
59. De Pastena M, Marchegiani G, Paiella S, et al. Impact of preoperative biliary drainage on postoperative outcome after pancreaticoduodenectomy: an analysis of 1500 consecutive cases. Dig Endosc. 2018;30:777–84.
60. Maggino L, Malleo G, Marchegiani G, et al. Outcomes of primary chemotherapy for borderline resectable and locally advanced pancreatic ductal adenocarcinoma. JAMA Surg. 2019;154(10):932–42.
61. Cloyd JM, Wang H, Egger ME, et al. Association of clinical factors with a major pathologic response following preoperative therapy for pancreatic ductal adenocarcinoma. JAMA Surg. 2017;152:1048–56.
62. Janssen QP, Buettner S, Suker M, et al. Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. J Natl Cancer Inst. 2019;111:782–94.

Chapter 46
Neoadjuvant and Adjuvant Radiotherapy in Operable Pancreatic Cancer

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Take Home Message

- There is increasing evidence to support the use of neoadjuvant concurrent chemoradiation or SBRT in borderline resectable and resectable pancreatic cancer.
- Neoadjuvant concurrent chemoradiation improves R0 resection rate, local control, and disease-free survival in borderline resectable pancreatic cancer; its clinical benefits in resectable pancreatic cancer remain to be proven.
- The role of adjuvant concurrent chemoradiation or SBRT in resected pancreatic cancer remains unclear.

Pearls and Pitfalls

- Published guidelines should be used consistently when assessing resectability.
- In borderline resectable and resectable pancreatic cancer, the patient's performance status, comorbidities, and preference should also be considered when making treatment decision with respect to neoadjuvant radiotherapy. For instance, radiotherapy should be avoided in patients with active connective tissue diseases or Crohn's disease.
- The duration of neoadjuvant treatment can be lengthy, patients should be restaged after completion of induction chemotherapy and then again after completion of concurrent chemoradiation or SBRT prior to surgery to rule out distant metastasis.

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Future Perspectives

- Future randomized phase III clinical trials should incorporate modern chemotherapy regimens such as mFOLFIRINOX or gemcitabine/nab-paclitaxel to assess the true benefit of neoadjuvant concurrent chemoradiation or SBRT in borderline resectable and resectable pancreatic cancer.
- With MR-LINAC-based adaptive radiotherapy, dose escalation may be achieved to control/ablate the tumor locally, thereby complementing systemic therapy and improving the clinical outcomes of pancreatic cancer patients.
- The potential therapeutic benefits of combining radiotherapy and targeted therapy/immunotherapy warrant further investigation.

46.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a therapeutic challenge in oncology. Surgical resection with negative margins (R0) is generally thought to be the only potentially curative treatment. Approximately 15–20% of PDAC patients have resectable disease, while the remaining have unresectable/locally advanced disease involving major abdominal vasculature or metastatic disease at the time of diagnosis [1].

PDAC patients who do not have distant metastasis are generally categorized into three groups based on the extent of involvement of major abdominal vasculature including the celiac axis, common hepatic artery, superior mesenteric artery/vein, and portal vein—resectable, borderline resectable, and unresectable/locally advanced.

The most recent criteria for defining resectability status and assigning patients to these three groups was published in the 2019 National Comprehensive Cancer Network (NCCN) clinical guidelines [2], which referenced the consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association [3]. The role of radiotherapy in these three groups of PDAC patients has been a matter of debate and is evolving rapidly with the advances in motion management, image guidance, and treatment techniques.

This chapter will focus on radiotherapy for PDAC in the neoadjuvant and adjuvant settings. The seminal clinical trials that support or challenge the incorporation of neoadjuvant and adjuvant radiotherapy in the management of borderline resectable and resectable PDAC will be reviewed to illustrate why this topic remains controversial and awaits further investigation. The potential of using technological advances in radiotherapy delivery and combining targeted therapy/immunotherapy with radiotherapy to improve clinical outcomes of PDAC will be discussed.

46.2 Neoadjuvant Radiotherapy in Borderline Resectable and Resectable Pancreatic Cancer

The use of neoadjuvant treatment in borderline resectable and resectable PDAC is gaining popularity and support (Box 46.1). Earlier clinical studies used chemotherapy alone or concurrent chemoradiation alone as neoadjuvant treatment, while more recent trials often incorporated induction chemotherapy followed by concurrent chemoradiation or stereotactic body radiotherapy (SBRT) alone.

Box 46.1 Rationale for Neoadjuvant Treatment

- Treating potential distant micrometastatic disease early
- Downstaging the primary tumor
- Improving resectability
- Eradicating micrometastatic disease in the operative field
- Increasing the probability of R0/N0 resection

A retrospective analysis of SEER data from close to 4000 resectable PDAC patients showed a survival benefit with neoadjuvant radiotherapy, with or without chemotherapy, compared to upfront surgery, with or without adjuvant treatment [4]. In a more recent meta-analysis, the Dutch Pancreatic Cancer Group [5] included 3484 patients with borderline resectable or resectable PDAC from 38 studies and compared neoadjuvant treatment with upfront surgery; neoadjuvant treatment involved chemotherapy alone, with gemcitabine used in the majority of studies, or concurrent chemoradiation with total radiation doses ranging from 30 to 54 Gy. It is noteworthy that this meta-analysis included studies reporting median overall survival in intention-to-treat analyses [5], which is in contrast to previous meta-analyses that might have introduced a survival bias by reporting outcomes only in patients who actually underwent surgical resection [6, 7]. The authors reported weighted median overall survival of 18.8 and 14.8 months, as well as R0 resection rate of 58.0% and 54.9% ($P = 0.088$) by intention-to-treat in patients who had neoadjuvant treatment and upfront surgery, respectively [5]. In patients who did undergo surgery, the R0 resection rate was higher (86.8% vs. 66.9%, $P < 0.001$), the pathological lymph node rate lower (64.8% vs. 43.8%, $P < 0.001$), and the weighted median overall survival longer (26.1 vs. 15.0 months) in the neoadjuvant treatment arm than in the upfront surgery arm [5]. Up to 64% of patients had at least grade 3 toxicity involving mostly leukopenia, thrombocytopenia, nausea, and fatigue [5].

A recent phase II/III trial [8] randomized 50 borderline resectable PDAC patients to neoadjuvant chemoradiation followed by surgery (n = 27) or upfront surgery (n = 23). Neoadjuvant chemoradiation was described as "a three-dimensional treatment plan of 45 Gy in 25 fractions and 9 Gy in five fractions (five times a week for a total of 6 weeks)" plus gemcitabine 400 mg/m^2 weekly. There was no detailed description of radiation treatment volumes with respect to gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) (Box 46.2), motion management, or image guidance.

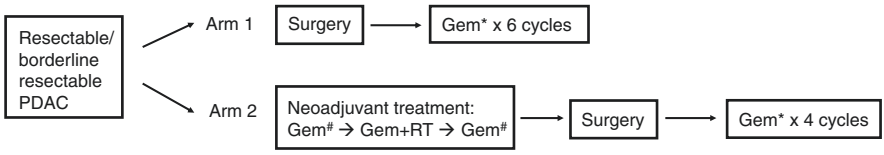
Box 46.2 Definitions of Radiotherapy Terminology[a]

Gross tumor volume (GTV)	The volume that contains gross disease that is palpable on clinical examination and/or is visualized on diagnostic imaging
Clinical target volume (CTV)	The volume that contains the GTV plus a margin to include any suspected microscopic disease; the CTV must receive the prescribed dose of radiation to achieve cure or palliation
Planning target volume (PTV)	The volume that contains the GTV and CTV plus a margin to account for all the uncertainties of treatment such as organ motion, patient motion, and irradiation geometry
Internal target volume (ITV)	The volume that encompasses the CTV and internal margin; internal margin accounts for the change in size, shape, and position of the CTV relative to anatomic reference points (e.g., movements of respiration, filling of duodenum)
Organs at risk (OAR)	Normal tissues with radiation sensitivity that may significantly affect treatment planning and/or prescribed dose

[a]Defined by the International Commission on Radiation Units and Measurements (ICRU) report 50 [9] and report 62 [10]

In the intention-to-treat analysis, significant improvements in 2-year survival rate and median survival (40.7% and 21 months vs. 26.1% and 12 months, HR 1.5, P = 0.028), as well as R0 resection rate (51.8% vs. 26.1%, P = 0.004) were reported in the neoadjuvant chemoradiation arm compared to the upfront surgery arm [8]. In those patients who underwent surgery, smaller tumor size (2.9 vs. 3.9 cm, P = 0.014), lower number of positive lymph nodes (0.5 vs. 1.9, P = 0.003), and lower total number of retrieved lymph nodes (19.1 vs. 30.7, P = 0.004) were also noted in the neoadjuvant chemoradiation arm than in the upfront surgery arm [8]. The overall recurrence rates were similar between the two arms, 88.2% vs. 88.9% in the neoadjuvant chemoradiation arm and the upfront surgery arm, respectively, with hepatic recurrence being the most common [8].

The PREOPANC trial, a multicenter randomized controlled phase III trial conducted by the Dutch Pancreatic Cancer Group, included 246 resectable and borderline resectable PDAC patients who were assigned to neoadjuvant treatment followed



Gem+RT = gemcitabine 1000 mg/m2 on day 1, 8, 15 + RT 36 Gyin 15 fractions, 2.4 Gyper fraction, over 3 weeks, followed by one week rest
Gem#= gemcitabine 1000 mg/m2 on day 1, 8, followed by one week rest
Gem* = gemcitabine 1000 mg/m2 on day 1, 8, 15, followed by one week rest

Fig. 46.1 Schema to PREOPANC trial 8. See text for supplemental information and results. *PDAC* pancreatic ductal adenocarcinoma, *Gem* gemcitabine, *RT* radiotherapy. Gem+RT = gemcitabine 1000 mg/m2 on day 1, 8, 15 + RT 36 Gy in 15 fractions, 2.4 Gy per fraction, over 3 weeks, followed by one week rest Gem# = gemcitabine 1000 mg/m^2 on day 1, 8, followed by one week rest Gem* = gemcitabine 1000 mg/m^2 on day 1, 8, 15, followed by 1 week rest

by surgery ($n = 119$) or upfront surgery ($n = 127$) (Fig. 46.1); both groups received adjuvant gemcitabine after surgery [11]. Radiotherapy was given to a total dose of 36 Gy in 15 fractions, 2.4 Gy per fraction over 3 weeks, concurrent with gemcitabine 1000 mg/m^2 weekly. Briefly, this trial used four-dimensional CT (4DCT) with intravenous contrast for radiation target delineation. GTV included the primary pancreatic tumor and pathological lymph nodes, CTV was a 5 mm expansion on the GTV, internal target volume (ITV) (Box 46.2) was the sum of CTVs from all phases of respiration, and PTV was a 10 mm expansion on the ITV; elective nodal regions were not covered [11]. At least 95% of the prescribed dose was to cover 98% of the PTV [11]. Results from this trial using intention-to-treat analyses showed significantly longer median disease-free survival (8.1 vs. 7.7 months, HR 0.73, $P = 0.032$) and locoregional failure-free interval (not reached vs. 13.4 months, HR 0.56, $P = 0.0034$), but not median distant metastasis-free interval (17.4 vs. 12.5 months, HR 0.82, $P = 0.24$) and median overall survival (16.0 vs. 14.3 months, HR 0.78, $P = 0.096$) in the preoperative chemoradiation group compared to the upfront surgery group [12]. In those patients who underwent surgery, significantly higher R0 resection rate (71% vs. 40%, $P < 0.001$), as well as lower rates of pathologic lymph nodes (33% vs. 78%, $P < 0.001$), perineural invasion (39% vs. 73%, $P < 0.001$), and venous invasion (19% vs. 36%, $P < 0.024$) were reported in the preoperative chemoradiation group than the upfront surgery group; and in those who had surgery followed by adjuvant chemotherapy, significantly longer median overall survival were observed in the former than the latter (35.2 vs. 19.8 months, HR 0.58, $P = 0.029$) [12]. Furthermore, neoadjuvant treatment (chemotherapy alone or radiation ± chemotherapy) was not associated with higher postoperative morbidity or mortality and importantly, neoadjuvant radiotherapy appeared to decrease the rates of pancreatic fistula and organ space infections postoperatively due to increased fibrosis [13–16]. Taken together, the aforementioned studies demonstrated promising clinical benefits and provided support for using concurrent chemoradiation in the neoadjuvant setting. Additional evidence will come from the randomized multicenter phase III NEOPA trial [17], which evaluates the impact of neoadjuvant concurrent chemoradiation (50.4 Gy in 28 fractions + gemcitabine 300 mg/m^2 weekly) on survival

compared to upfront surgery in resectable and borderline resectable adenocarcinoma of the pancreatic head/uncinate process, and is expected to conclude in 2020.

The American Society for Radiation Oncology (ASTRO) published the 2019 clinical practice guidelines for radiation therapy in pancreatic cancer [18], which conditionally recommended neoadjuvant therapy without mentioning specific regimens for patients with resectable disease, recognizing the low quality of available evidence and suggesting neoadjuvant therapy to be offered on a clinical trial basis. For patients with borderline resectable PDAC, the 2019 ASTRO clinical practice guidelines conditionally recommended systemic chemotherapy followed by concurrent chemoradiation using conventional fractionation regimens or multifraction SBRT alone [18]. The 2019 NCCN clinical guidelines [2] listed (m)FOLFIRINOX or gemcitabine/nab-paclitaxel ± subsequent concurrent chemoradiation as the preferred neoadjuvant therapy regimens, and capecitabine or infusional 5-FU as the preferred agents to be used concurrently with radiation. The 2019 NCCN guidelines [2] also included neoadjuvant therapy and consideration of neoadjuvant therapy (particularly in high risk patients such as those with large primary tumor or very high CA19-9) as part of the treatment pathway for borderline resectable and resectable PDAC, respectively. The European Society for Radiotherapy and Oncology (ESTRO) has not published clinical practice guidelines for radiation therapy in pancreatic cancer.

The radiation dose fractionation, target volumes, and techniques currently used in the neoadjuvant setting for borderline resectable and resectable PDAC are often institution dependent. As mentioned above, total radiation doses ranging from 30 to 54 Gy have been used in the published literature [5]. The total radiation dose and dose per fraction are limited by the tolerance of surrounding organs at risk (OAR) (Box 46.2), including stomach, duodenum, small bowel, large bowel, liver, kidneys, and spinal cord in the context of pancreatic cancer radiotherapy. Total radiation doses of 30–54 Gy is acceptable from the perspectives of achieving the goals of neoadjuvant treatment (Box 46.1) and minimizing the acute/late side effects of radiation to the OAR. When delivered concurrently with radiosensitizing chemotherapy agents such as gemcitabine or capecitabine, conventional fractionation radiotherapy to a total dose of 50.4 Gy in 28 fractions, 1.8 Gy per fraction daily, over 5.5 weeks is the most commonly used regimen (Fig. 46.2).

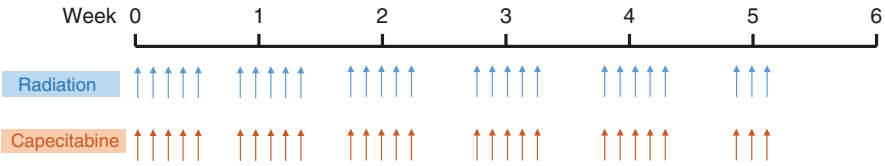


Fig. 46.2 Most commonly used concurrent chemoradiation regimen. Radiation is given as 1.8 Gy fraction (blue arrows) once daily, 5 days per week, to a total dose of 50.4 Gy, over 5.5 weeks. The chemotherapy agent that is used concurrently with radiation varies from institution to institution. Capecitabine, given at 1000 mg/m^2 PO bid (orange arrows), on days of radiation is shown here as an example

A single-institution retrospective study ($n = 472$) from the MD Anderson Cancer Center (MDACC) [19] demonstrated no significant difference in R1 margin status, treatment effect, local recurrence, and overall survival between preoperative standard fractionation radiotherapy (50.4 Gy in 28 fractions) and hypofractionation radiotherapy (30 Gy in 10 fractions) given concurrently with chemotherapy (5-FU, capecitabine, or gemcitabine); however, the 50.4 Gy regimen was associated with higher N0 rate (53.8% vs. 41.1%, $P < 0.01$) and lower mean lymph node ratio (0.06 vs. 0.09, $P < 0.01$) compared to the 30 Gy regimen. Local recurrence rate was lower in patients who received neoadjuvant concurrent chemoradiation than in those who received neoadjuvant chemotherapy alone (22% vs. 33%, $P < 0.01$) [19]. This retrospective study included PDAC patients with resectable, borderline resectable, and locally advanced disease. The CTV included the primary tumor and regional lymph nodes with a 1 cm margin, CTV-to-PTV margin was 5 mm; three-dimensional conformal radiotherapy was used [19].

Prospective studies have been small phase II trials, with an MDACC trial ($n = 86$) [20] using 30 Gy in ten fractions concurrent with gemcitabine 400 mg/m^2 weekly and showing a median survival of 34.0 months and 5-year survival rate of 36% in resectable PDAC patients who underwent surgery, and a German trial ($n = 73$) [21] using 45–57.6 Gy in 1.8 Gy fractions concurrent with gemcitabine (300 mg/m^2)/cisplatin (30 mg/m^2) on day 1, 8, 22, 29 of radiation and reporting similar R0 resection rates (52% vs. 48%, $P = 0.81$), time to progression (8.4 vs. 8.7 months, $P = 0.95$), and median overall survival (25.0 vs. 18.9 months, $P = 0.79$) in resectable PDAC patients who had neoadjuvant chemoradiation followed by surgery vs. those who had surgery alone, respectively. Both the MDACC and the German prospective phase II studies covered elective nodal regions and used three-dimensional conformal radiation [20, 21]. A more recent single-arm, phase II trial from the Massachusetts General Hospital (MGH) treated 48 patients with borderline resectable PDAC with induction FOLFIRINOX followed by neoadjuvant concurrent chemoradiation (25 Gy in five fractions with protons, or 30 Gy in ten fractions or 58.8 Gy in 28 fractions with photons + capecitabine 825 mg/m^2 bid on days of radiation), and reported a R0 resection rate of 97%, 2-year progression-free survival of 55%, and 2-year overall survival of 72% [22]. CTV included GTV with 1-cm margin and elective nodal regions in the MGH study [22]. It is presently unclear what the optimal radiation dose fractionation is and whether elective nodes should be covered intentionally for neoadjuvant concurrent chemoradiation in borderline resectable and resectable PDAC.

SBRT alone, with no concurrent chemotherapy, is also a neoadjuvant treatment option. SBRT refers to the delivery of large doses of radiation, usually in 1–5 fractions, to the target precisely, with the high dose volume conforming closely to the target and rapid dose fall-off away from the target [23]. A representative SBRT plan for the treatment of adenocarcinoma of the pancreatic body is shown in Fig. 46.3. Mellon et al. [24] previously reported R0 resection rate of 96% and median overall survival of 19.2 months in borderline resectable PDAC patients ($n = 110$) who received induction gemcitabine-based chemotherapy followed by neoadjuvant SBRT; any grade 3 or higher radiation-related toxicity was 7%. Furthermore,

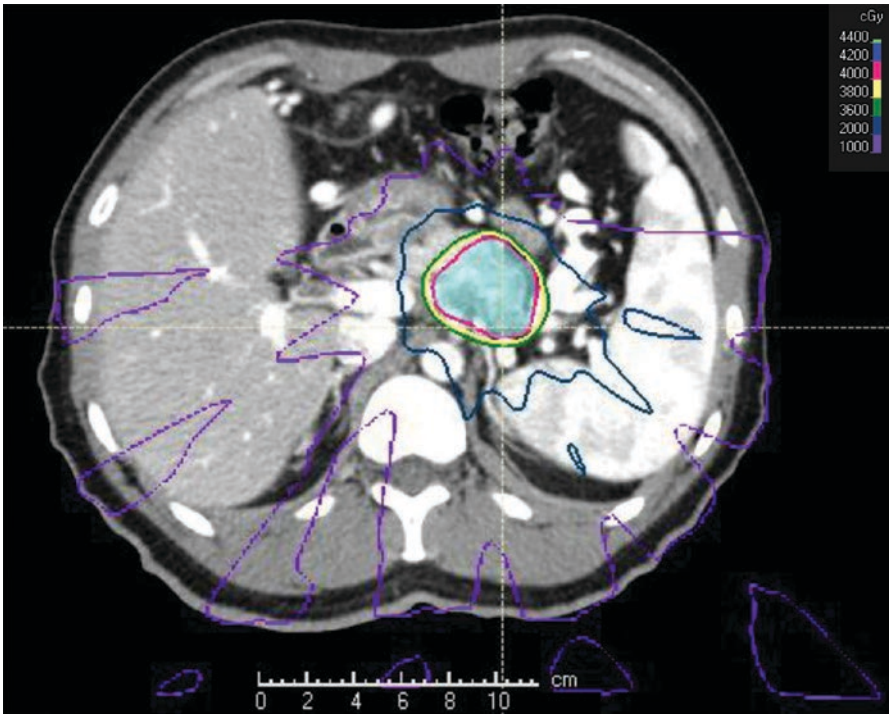


Fig. 46.3 SBRT plan for the treatment of adenocarcinoma of the pancreatic body. The prescribed dose was 40 Gy in five fractions. Planning target volume (PTV), light blue colour wash. Different coloured lines represent different isodose levels as indicated by the scale in the top right corner. Note how the 40 Gy isodose line (pink) conforms to the PTV and the rapid dose fall-off away from the PTV

borderline resectable PDAC patients who demonstrated sufficient response to such neoadjuvant treatment were shown to have similar perioperative and long-term survival outcomes to their resectable counterparts [25]. The PTV received 28–30 Gy in five fractions and the areas of vessel involvement (aka tumor vessel interface) received a simultaneous boost of up to 50 Gy; the GTV-to-PTV margin was 3–5 mm [24]. The Alliance A021501 trial evaluated induction mFOLFIRINOX (modified 5-FU/irinotecan/oxaliplatin) followed by mFOLFIRINOX ± SBRT prior to surgery in borderline resectable PDAC patients [26], the results of which are expected to shed more light on the role of SBRT in the neoadjuvant setting. Neoadjuvant SBRT has several advantages—it is convenient to patients (3–5 fractions vs. 28 fractions with conventional fractionation radiotherapy), limits the delay for further systemic therapy or surgery, provides good local control, allows radiation dose escalation at tumor-vessel interface and thereby increases R0 resection rate, and provides greater cost-effectiveness in terms of quality adjusted life years [27].

It should be emphasized that all of the aforementioned meta-analyses and clinical studies, with the exceptions of the Alliance A021501 trial [26] and the MGH

phase II trial [22], were either concluded or conceived in the pre-(m)FOLFIRINOX and gemcitabine/nab-paclitaxel era. Therefore, the results cannot be extrapolated to the modern day neoadjuvant setting when induction (m)FOLFIRINOX or gemcitabine/nab-paclitaxel often precedes neoadjuvant concurrent chemoradiation or SBRT. Additional prospective randomized trials that consistently adopt the NCCN criteria [2] for defining resectability status and incorporate these modern chemotherapy regimens should be pursued in order to determine the true benefit of neoadjuvant concurrent chemoradiation or SBRT in the borderline resectable cohort and the resectable cohort separately.

The 2019 ASTRO clinical practice guidelines [18] conditionally recommended 45–50.4 Gy in 1.8–2 Gy fractions for borderline resectable patients who are undergoing neoadjuvant concurrent chemoradiation, and 30–33 Gy in 6–6.6 Gy fractions with a consideration to boost the tumor vessel interface simultaneously to 40 Gy for those who are undergoing neoadjuvant SBRT alone. For conventional fractionation radiotherapy, there is no published consensus panel guidance for target volumes in the neoadjuvant setting; the target volumes from the PREOPANC trial [11] or the MDACC study [19] described above may be used. For SBRT, the 2019 ASTRO clinical practice guidelines [18] strongly recommended including the GTV with a small margin in the treatment volume and not routinely treating elective lymph nodes. With respect to radiation planning, the 2019 ASTRO clinical practice guidelines [18] strongly recommended the use of the following: patient-specific motion management techniques such as 4DCT simulation, intravenous contrast at simulation, daily imaging guidance such as cone beam CT or CT-on-rail, fiducial placement especially for SBRT, and modulated treatment techniques such as intensity modulated radiotherapy or volumetric modulated arc therapy. These radiation planning techniques allow better target delineation, superior target conformality and normal tissue sparing, and more precise treatment delivery, potentially maximizing local control and minimizing acute/late toxicities.

46.3 Adjuvant Radiotherapy in Resected Pancreatic Cancer

The clinical benefit of adjuvant concurrent chemoradiation in resected PDAC is a matter of controversy [28]. Earlier studies including GITSG 91-73 [29] and EORTC 40891 [30, 31] were conducted in the 1980s and 1990s, with the former reporting significant improvements in median survival (20 vs. 11 months) and 2-year overall survival (42% vs. 15%) in patients who received adjuvant chemoradiation compared to those who did not, and the latter in a 12-year update showing no significant 10-year overall survival (17% vs. 18%) and progression-free survival (16% vs. 17%) benefits with adjuvant chemoradiation vs. observation. Bolus 5-FU and infusional 5-FU were used in the GITSG 91-53 and EORTC 40891 studies, respectively. The GITSG 91–73 study included patients who underwent subtotal (68%) or total (32%) pancreatectomy and had negative resection margins, and excluded patients with periampullary cancer; radiation volumes included the pancreas, pancreatic

bed, and regional lymph nodes and were treated with parallel opposed beams [29]. On the other hand, the EORTC 40891 study included patients with periampullary adenocarcinoma (who generally have better prognosis) and patients with both positive and negative resection margins; radiation volumes and techniques were not described in detail [30, 31]. GITSG 91-73 patients received maintenance chemotherapy while EORTC 40891 patients did not. As such, direct comparison between the two trials cannot be made.

Subsequently, the ESPAC-1 trial randomized patients resected for PDAC ($n = 541$) with negative and positive margins to adjuvant chemoradiation or chemotherapy, or by the clinician's choice in a 2 × 2 factorial design of observation, adjuvant chemoradiation alone, chemotherapy alone, or both [32, 33]. In patients who received both adjuvant chemoradiation and chemotherapy, chemoradiation was administered before chemotherapy. The 5-year survival rate was significantly higher in the patients who received adjuvant chemotherapy than those who did not (21% vs. 8%, $P = 0.009$), while the 5-year survival rates were significantly lower in the patients who received adjuvant chemoradiation before chemotherapy than those who did not (10% vs. 20%, $P = 0.05$) [33]. The ESPAC-1 trial has several limitations: selection bias due to clinician choice of randomization and "background" treatment, lack of central quality assurance for radiotherapy, inconsistent radiation dose, and approximately 1/3 of the patients in the observation and chemotherapy arms received radiotherapy. Stocken et al. [34] performed a meta-analysis of five randomized trials including the GITSG 91-73, EORTC 40891, and ESPAC-1 studies ($n = 875$ in total), and found that adjuvant chemotherapy significantly decreases the risk of death by 25% (HR 0.75, $P = 0.001$), while adjuvant 5-FU based chemoradiation does not (HR 1.09, $P = 0.43$). However, subgroup analyses suggested that chemoradiation may be more effective and chemotherapy less effective in patients with positive resection margins [34]. It is important to emphasize that the GITSG 91-73, EORTC 40891, and ESPAC-1 studies used the concurrent chemoradiation regimen of 40 Gy split course (20 Gy in ten fractions +5-FU) with a 2-week break in between and outdated radiation techniques. This split course radiation regimen is unlikely to provide adequate locoregional control and is no longer standard practice. As such, findings from these historical studies should not form the basis of the arguments for or against the use of adjuvant concurrent chemoradiation for resected PDAC.

The RTOG 97-04 study [35, 36] is a phase III trial ($n = 451$) comparing the efficacy of adjuvant 5-FU vs. gemcitabine given before and after concurrent chemoradiation in PDAC patients who had gross total resection. Concurrent chemoradiation consisted of 50.4 Gy in 28 fractions + infusional 5-FU 250 mg/m^2/day. This trial reported no difference in survival between adjuvant 5-FU and gemcitabine and greater hematological toxicity with gemcitabine. However, the updated analysis of this trial [37] showed that radiotherapy quality assurance and protocol compliance were associated with improved median survival and decreased risk of locoregional failure in all patients, and decreased grade 4/5 non-hematological toxicity in gemcitabine patients. Worse survival was also noted in patients with post-operative CA19-9 > 90 U/mL (HR 3.1, $P < 0.0001$) [38]. Furthermore, a multi-institutional

retrospective pooled analysis ($n = 955$) showed significant improvements in median overall survival (39.9 vs. 27.8 months, $P < 0.001$) and 5-year survival rate (41.2% vs. 25.7%, $P < 0.001$) in patients treated with adjuvant concurrent chemoradiation with or without adjuvant chemotherapy compared to those treated with adjuvant chemotherapy alone [39]. Concurrent chemoradiation in this analysis consisted of 50.4 Gy in 28 fractions in most centers, 45 Gy in 25 fractions in two centers, and 54–60 Gy in 27–30 fractions in one center using multiple-field techniques with no planned break to be given concurrently with 5-FU, capecitabine, gemcitabine or tegafur [39].

The EORTC 40013-22012 phase II study ($n = 90$) demonstrated no difference in disease-free survival and overall survival in resected patients who received four cycles of adjuvant gemcitabine alone vs. those who received two cycles of adjuvant gemcitabine followed by concurrent chemoradiation (50.4 Gy in 28 fractions + gemcitabine 300 mg/m^2 weekly) [40], although the rate of local recurrence alone as first progression was lower in the latter than the former (11% vs. 24%).

On the other hand, the Johns Hopkins Hospital-Mayo Clinic collaborative study ($n = 1092$) [41] showed significant improvement in overall survival with adjuvant chemoradiation (50.4 Gy in 28 fractions +5-FU) compared to surgery alone (21.1 vs. 15.5 months, $P < 0.001$), although no adjuvant chemotherapy alone arm was present.

The RTOG 08-48 trial is a phase III trial designed to evaluate if adding erlotinib to gemcitabine confers survival benefits compared to gemcitabine alone, and to assess whether adding chemoradiation in the absence of disease progression after a full course of gemcitabine is superior to a full course of gemcitabine alone in patients who have undergone R0 or R1 resection [28]. Although the RTOG 08-48 trial incorporated modern radiation doses and treatment techniques, it did not incorporate (m)FOLFIRINOX or gemcitabine/nab-paclitaxel as the adjuvant systemic treatment regimen. Therefore, the results from this trial when available should also be interpreted with caution.

While SBRT (20–24 Gy in one fraction or 30 Gy in three fractions) can be delivered safely in resected PDAC with close or positive margins based on a single-institution study [42], there is currently no evidence to support the use of adjuvant SBRT. Similar to the neoadjuvant setting, clinical trials that incorporate modern radiation dose fractionation and treatment techniques as well as contemporary systemic therapies are sorely needed to address the role of adjuvant concurrent chemoradiation or SBRT in resected PDAC.

The 2019 ASTRO clinical practice guidelines [18] conditionally recommended adjuvant concurrent chemoradiation (45–54 Gy in 1.8–2 Gy fractions +5-FU based chemotherapy) in patients with high risk resected disease (positive lymph nodes and margins), strongly recommended 4–6 months of systemic chemotherapy followed by concurrent chemoradiation in patients with resected disease undergoing adjuvant treatment and the use of the NRG Oncology consensus panel guidance for CTV delineation [43]. The radiation planning recommendations for adjuvant treatment are similar to those described above for neoadjuvant treatment.

46.4 Future Directions

46.4.1 Utilizing Technological Advances to Improve Radiotherapy Delivery

MR-LINAC combines high resolution magnetic resonance imaging with a linear accelerator into a single machine (Fig. 46.4), allowing radiation oncologists to track and monitor the day to day motion of the tumor and normal tissues in real time with better resolution and no added radiation dose to the patient [44]. It is particularly useful in upper abdominal radiotherapy for pancreatic cancer given the superior soft tissue contrast with MR imaging and the highly variable daily physiological changes of luminal gastrointestinal tissues. A pancreatic head tumor is in close proximity to the duodenum, small bowel and stomach. Cone beam CT (CBCT) is suboptimal for daily treatment verification especially in the absence of fiducials because the pancreatic tumor and luminal gastrointestinal tissues are virtually indistinguishable from each other on CBCT. Day to day changes in the distension of luminal gastrointestinal tissues can have profound effects on treatment efficacy and toxicity. Therefore, it is conceivable that with MR-LINAC-based adaptive radiotherapy, dose escalation may be achieved using hypofractionation or SBRT to control/ablate the tumor locally, thereby complementing systemic therapy and improving the clinical outcomes of pancreatic cancer patients.

Fig. 46.4 MR-LINAC combines high resolution magnetic resonance imaging with a linear accelerator into a single machine. Photo Courtesy Sunnybrook Health Sciences Center Department of Radiation Oncology, Toronto, Canada

46.4.2 Targeted Therapy and Immunotherapy in Combination with Radiotherapy

To improve the therapeutic index of radiotherapy, better visualization for physical tumor targeting and normal tissue avoidance during each fraction through image-guided radiotherapy is only one piece of the puzzle. Using pharmacological agents to enhance tumor cell kill by radiation and/or to mitigate the acute/late toxicities of radiation on normal tissues, and identifying biomarkers to select PDAC patients who are most likely to benefit from radiotherapy are the other pieces towards improving clinical outcomes.

The synergy between radiotherapy and immunotherapy is an area of substantial interest and active investigation in radiation oncology [45]. Wild et al. [46] previously reported inferior survival in locally advanced PDAC patients with total lymphocyte count of <500 cells/mm^3 2 months after starting conventional fractionation radiotherapy given concurrently with 5-FU, capecitabine, or gemcitabine. In a subsequent study by the same group [47], SBRT was found to induce significantly less severe lymphopenia compared to conventional fractionation radiotherapy with concurrent chemotherapy. Lymphocytes are some of the most radiosensitive cells in the body. Direct toxicity to the lymphocytes as they traverse through the irradiated field in the circulation is likely the cause of radiation-induced lymphopenia. The lymphocyte sparing effect of SBRT appeared to be independent of the use of chemotherapy, and could be attributed to smaller irradiated tissue and blood volume during SBRT [47, 48]. This makes SBRT a logical and attractive radiation treatment technique to be evaluated in combination with immunotherapy as lymphocytes are required for immuno-oncologic agents such as checkpoint inhibitors to exert their antitumor effects.

Radiation induces both immuostimulation and immunosuppression [48–50]. PDAC does not appear to be particularly immunogenic. The interactions between radiation and the immune system are complex. Total radiation dose, dose per fraction, field size, and treatment techniques will invariably affect these interactions and in turn modify tumor response to treatment. Future clinical trials that investigate the toxicity and efficacy of combining radiotherapy and immunotherapy should incorporate the evaluation of dose fractionation and field size effects and the use of plasma and/or imaging biomarkers to identify PDAC patients who are most likely benefit from such combination.

46.5 Conclusion

There is increasing evidence to support the use of neoadjuvant concurrent chemoradiation or SBRT in borderline resectable and resectable pancreatic cancer. Adjuvant concurrent chemoradiation remains a subject of controversy. The majority of current published literature used old chemotherapy regimens and sometimes outdated

radiotherapy techniques/dose fractionation and therefore, should be interpreted with caution. Prospective randomized clinical trials that consistently adopt established criteria of defining resectability status and incorporate (m)FOLFIRINOX or gemcitabine/nab-paclitaxel and modern radiotherapy techniques/dose fractionation are sorely needed to evaluate the true benefit of neoadjuvant concurrent chemoradiation or SBRT in borderline resectable and resectable pancreatic cancer. The potential therapeutic benefits of using MR-LINAC for radiotherapy delivery and combining radiotherapy and targeted therapy/immunotherapy warrant further investigation.

References

1. Heinrich S, et al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26:2526–31.
2. https://www.nccn.org/professionals/physician_gls/default.aspx
3. Al-Hawary MM, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the American pancreatic association. Gastroenterology. 2014;146:291–304.e1.
4. Stessin AM, et al. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. Int J Radiat Oncol Biol Phys. 2008;72:1128–33.
5. Versteijne E, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105:946–58.
6. Gillen S, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7:e1000267.
7. Laurence JM, et al. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. J Gastrointest Surg. 2011;15:2059–69.
8. Jang J-Y, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268:215–22.
9. ICRU. Report 50: prescribing, recording, and reporting photon beam therapy. Washington, DC: International Commission on Radiation Units and Measurements; 1993.
10. ICRU. Report 62: prescribing, recording, and reporting photon beam therapy. Washington, DC: International Commission on Radiation Units and Measurements; 1999.
11. Versteijne E, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. Trials. 2016;17:127.
12. Versteijne E, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020; https://doi.org/10.1200/JCO.19.02274.
13. Ishikawa O, et al. Concomitant benefit of preoperative irradiation in preventing pancreas fistula formation after pancreatoduodenectomy. Arch Surg. 1991;126:885–9.
14. Takahashi H, et al. Preoperative chemoradiation reduces the risk of pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. Surgery. 2011;150:547–56.
15. Cooper AB, et al. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? J Gastrointest Surg. 2015;19:80–6; discussion 86–7

16. Denbo JW, et al. Preoperative chemoradiation for pancreatic adenocarcinoma does not increase 90-day postoperative morbidity or mortality. J Gastrointest Surg. 2016;20:1975–85.
17. Tachezy M, et al. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA-a randomized multicenter phase III study (NCT01900327, DRKS00003893, ISRCTN82191749). BMC Cancer. 2014;14:411.
18. Palta M, et al. Radiation therapy for pancreatic cancer: executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol. 2019;9:322–32.
19. Cloyd JM, et al. Impact of hypofractionated and standard fractionated chemoradiation before pancreatoduodenectomy for pancreatic ductal adenocarcinoma. Cancer. 2016;122:2671–9.
20. Evans DB, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26:3496–502.
21. Golcher H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015;191:7–16.
22. Murphy JE, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2018;4:963–9.
23. Benedict SH, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010;37:4078–101.
24. Mellon EA, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol. 2015;54:979–85.
25. Mellon EA, et al. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. J Gastrointest Oncol. 2016;7:547–55.
26. Katz MHG, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. BMC Cancer. 2017;17:505.
27. Rosati LM, et al. Integration of stereotactic body radiation therapy into the multidisciplinary management of pancreatic cancer. Semin Radiat Oncol. 2017;27:256–67.
28. Chuong MD, et al. Adjuvant chemoradiation for pancreatic cancer: what does the evidence tell us? Gastrointest Oncol. 2014;5:166–77.
29. Kalser MH, et al. Pancreatic cancer. Assessment of prognosis by clinical presentation. Cancer. 1985;56:397–402.
30. Klinkenbijl JH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230:776–82; discussion 782–4.
31. Smeenk HG, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007;246:734–40.
32. Neoptolemos JP, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358:1576–85.
33. Neoptolemos JP, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350:1200–10.
34. Stocken DD, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005;92:1372–81.
35. Regine WF, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299:1019–26.
36. Regine WF, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18:1319–26.

37. Abrams RA, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys. 2012;82:809–16.
38. Berger AC, et al. Five year results of US intergroup/RTOG 9704 with postoperative CA 19-9 ≤90 U/mL and comparison to the CONKO-001 trial. Int J Radiat Oncol Biol Phys. 2012;84:e291–7.
39. Morganti AG, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys. 2014;90:911–7.
40. Van Laethem J-L, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. J Clin Oncol. 2010;28:4450–6.
41. Hsu CC, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol. 2010;17:981–90.
42. Rwigema JC, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close of positive margins. J Gastrointest Cancer. 2012;43:70–6.
43. Goodman KA, et al. Radiation Therapy Oncology Group consensus panel guidelines for the delineation of the clinical target volume in the postoperative treatment of pancreatic head cancer. Int J Radiat Oncol Biol Phys. 2012;83:901–8.
44. Hall WA, et al. The transformation of radiation oncology using real-time magnetic resonance guidance: a review. Eur J Cancer. 2019;122:42–52.
45. Grassberger C, et al. Assessing the interactions between radiotherapy and antitumour immunity. Nat Rev Clin Oncol. 2019;16:729–45.
46. Wild AT, et al. The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. Am J Clin Oncol. 2015;38:259–65.
47. Wild AT, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2016;94:571–9.
48. Ellsworth SG. Field size effects on the risk and severity of treatment-induced lymphopenia in patients undergoing radiation therapy for solid tumors. Adv Radiat Oncol. 2018;3:512–9.
49. Demaria S, et al. The optimal partnership of radiation and immunotherapy: from preclinical studies to clinical translation. Radiat Res. 2014;182:170–81.
50. Demaria S, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004;58:862–70.

Chapter 47
Preoperative Therapy in Patients with Borderline Resectable and Locally Advanced Pancreatic Cancer

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Take Home Messages

- Preoperative chemotherapy in patients with borderline resectable and locally advanced pancreatic cancer may result in downstaging of the tumor, increasing the likelihood of a radical resection.
- There is increasing evidence from randomized trials that preoperative chemoradiotherapy compared with upfront surgery improves survival in patients with (borderline) resectable pancreatic cancer.
- CT scans are mostly unable to differentiate between tumour tissue and fibrosis following preoperative chemo(radio)therapy and hereby underestimate the impact of preoperative therapy in locally advanced and borderline resectable pancreatic cancer.

Pearls and Pitfalls

- Preoperative chemotherapy in patients with borderline resectable and locally advanced pancreatic cancer may result in downstaging of the tumor, increasing the likelihood of a radical resection.

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- CT scans are mostly unable to differentiate between tumour tissue and fibrosis following preoperative chemo(radio)therapy in patients with borderline resectable and locally advanced pancreatic cancer.
- CA-19.9 response is very useful in selecting patients with borderline resectable and locally advanced pancreatic cancer following preoperative chemotherapy

Future Perspectives
- Trials using preoperative FOLFIRINOX chemotherapy for (borderline) resectable pancreatic cancer are ongoing.
- The added value of radiotherapy to chemotherapy in the preoperative setting remains uncertain and needs to be evaluated in future trials.

47.1 Locally Advanced and Borderline Resectable Pancreatic Cancer

Of all patients diagnosed with pancreatic cancer, over 50% have metastatic disease at onset and 30–40% have extensive vascular involvement which makes radical resection impossible as primary treatment [1]. Locally advanced pancreatic cancer (LAPC) is defined as a pancreatic adenocarcinoma without distant metastasis, but with involvement of the hepatic artery, superior mesenteric artery, celiac trunk or involvement of the porto-mesenteric vein that is considered not eligible for resection and reconstruction [2].

Borderline resectable pancreatic cancer (BRPC) is technically considered resectable, although the vascular involvement will reduce the likelihood of an R0-resection. Consensus on resectability criteria is currently lacking and also influenced by the local philosophy and experience per center. The different definitions for borderline resectable pancreatic cancer are listed in Table 47.1 [3, 4].

Radical resection (R0-resection, i.e. a tumor-free resection margin >1 mm [5]) is an important predictor for long-term survival of pancreatic cancer [6]. Unfortunately, only 20% of all patients are considered feasible for upfront resection at diagnosis. Recent studies have demonstrated that in 10–25% of the patients who are considered unresectable, an R0-resection can be achieved after induction chemotherapy treatment, known as conversion surgery [4].

Considerable developments in preoperative therapy have demonstrated better response rates in LAPC and BRPC with regards to inducing tumor regression and treatment of micrometastatic lesions, which makes R0-resection more likely [7, 8]. In selected patients, surgery after preoperative chemotherapy in locally advanced disease may achieve similar or even superior survival rates as those obtained in upfront resectable pancreatic cancer [9, 10]. Besides, preoperative chemotherapy can be helpful in filtering out patients with biologically aggressive disease, who would otherwise have rapid progression shortly after surgery [7]. Therefore

Table 47.1 Various definitions of borderline resectable pancreatic cancer

	Porto-mesenteric vein	Superior mesenteric artery	Celiac artery	Hepatic artery
AHPBA/ SSAT/SSO/ NCCN*	Encasement, abutment, impingement or occlusion of a short segment	Abutment	Uninvolved	Abutment or encasement of short segment
Alliance	≥180° circumference or reconstructable occlusion	<180° circumference	<180° circumference	Considered reconstructable, any degree of circumference
MD Anderson	Occlusion	Abutment	Abutment	Short segment encasement or abutment
Dutch Pancreatic Cancer Group	90–270° circumference	1–90° circumference	1–90° circumference	1–90° circumference

*AHPBA/SSAT/SSO/NCCN: Americas Hepato-Pancreato-Biliary Association/ Society for Surgery of the Alimentary Tract/ Society of Surgical Oncology/National Comprehensive Cancer Network; Alliance: Alliance for Clinical Trials in Oncology

preoperative therapy is currently considered by most surgeons as the standard treatment in LAPC and BRPC [11].

47.2 Staging and Diagnosis

47.2.1 Imaging

For the staging of pancreatic cancer, CT scan is currently considered the most optimal imaging modality [4]. Additionally, an MRI scan may detect and characterize small liver lesions that could be metastases, although the clinical impact of MRI has not been assessed by randomized studies [12]. PET scans are not recommended as routine diagnostic imaging in most countries, although it is included in the UK NICE guideline [13].

47.2.2 Diagnosis

Prior to start of preoperative treatment, the diagnosis should ideally be confirmed by histopathological analysis by obtaining tissue with fine needle aspiration (FNA) using endoscopic ultrasound [4]. If however FNA is not possible, an alternative way to collect tissue is endoscopically performing intraductal biopsy or brushing during endoscopic retrograde cholangiopancreaticoscopy (ERCP) [14]. Ultrasound or

CT-guided biopsy may be required to confirm extraregional lymph node metastases. In situations where no preoperative treatment is given, upfront surgery without histopathological confirmation is also optional.

47.2.3 CA19-9

Prior to start of preoperative chemotherapy a baseline Carbohydrate Antigen 19-9 (CA19-9) is measured in order to evaluate the response to treatment. One should take notice that CA19-9 can only reliably be determined after obstructive jaundice subsides [4]. As such, CA19-9 is mostly a useful biomarker for monitoring effect of chemotherapy and post-operative follow up [15], to monitor biochemical response.

Notably, approximately 5–10% of individuals do not produce CA19-9 due to a missing Lewis antigen [16]. Therefore CA19-9 is mostly only of use in patients with an elevated baseline value prior to start of preoperative treatment.

47.2.4 Baseline Conditions

It is important to ascertain baseline conditions in order to decide what regimen of chemotherapy is most appropriate. Adequate renal, liver and hematologic function (serum platelets, neutrophil count) should be confirmed prior to start of chemotherapy, and be monitored carefully during treatment.

For the administration of FOLFIRINOX, serum bilirubin levels may not.

exceed 1.5 times the upper limit of normal, because of the hepatic toxicity of this regimen [17]. Most patients with pancreatic head cancer therefore require some form of biliary drainage before the start of chemotherapy administration.

47.2.5 Diagnostic Laparoscopy

A diagnostic laparoscopy (DLS) can identify occult peritoneal or superficial liver metastasis in patients with LAPC and BRPC. Diagnostic laparoscopy, prior to start of treatment, may determine metastases in three out of 25 patients without radiological signs of metastatic disease [18]. A previous meta-analysis including 242 patients with LAPC demonstrated occult metastatic disease in 86 patients (36%) upon diagnostic laparoscopy either before or after preoperative treatment [19].

However, consensus is lacking in what stage of treatment a diagnostic laparoscopy best is performed. Some centers perform a DLS ahead of preoperative treatment whereas others perform DLS just prior to surgical exploration, often in the same surgical setting.

47.3 Choice of Preoperative Treatment

Various schemes of chemotherapy with or without radiation therapy (i.e. chemoradiotherapy) are administered as preoperative treatment for LAPC and BRPC. Primarily, gemcitabine monotherapy was the most prevelant administered regimen in pancreatic cancer. However, since the study by Conroy et al. showed superior outcomes of FOLFIRINOX compared with gemcitabine monotherapy in patients with metastatic disease in 2011 [20], these results are also extrapolated to BRPC and LAPC. Eversince, FOLFIRINOX is also administered to patients with LAPC and BRPC as preoperative treatment, despite a lack of randomized studies in this setting [21]. Trials that use FOLFIRINOX in the preoperative setting are ongoing [22].

For patients who are expected not to tolerate FOLFIRINOX, gemcitabine plus nab-paclitaxel can be administered. Similar to FOLFIRINOX, the superiority of gemcitabine nab-paclitaxel over gemcitabine monotherapy is only demonstrated in metastatic pancreatic cancer [23]. Nevertheless, published cohort studies report promising results of preoperative gemcitabine nab-paclitaxel in locally advanced and borderline resectable pancreatic cancer [24].

Combinations of chemotherapy and radiotherapyare traditionally widely used in this setting. Preoperative chemoradiotherp schedules are usually gemcitabine or 5-FU based. Currently, studies are ongoing combining FOLFIRINOX or gemcitabine NabPaclitaxel with, for instance, steroeotactic radiation.

47.3.1 Types of Chemotherapy

FOLFIRINOX is a combination of fluorouracil, leucovorin, oxaliplatin and irinotecan. Irinotecan has synergistic activity with fluorouracil and leucovorin against pancreatic cancer. Oxaliplatin only demonstrates activity against pancreatic cancer when administered in combination with fluorouracil [25].

Preoperative chemotherapy with FOLFIRINOX is generally advised for 4–8 cycles which can be administered in 2–4 months, however consensus is still lacking concerning the optimal duration of induction chemotherapy. FOLFIRINOX is administered in a two weekly schedule starting with the infusion of oxaliplatin in 2 h (85 mg/m^2), followed by 2 h infusion of folinic acid (400 mg/m^2) and infusion of irinotecan (180 mg/m^2). Subsequently fluoracil is administered starting with a bolus (400 mg/m^2) followed by 46 h continuous infusion (2400 mg/m^2). However based on local standards, the doses of FOLFIRINOX are often or even routinely reduced.

Gemcitabine and nab-paclitaxel is administered on days 1, 8 and 15 in every cycle of 4 weeks. Nab-paclitaxel is administered at a dose of 125 mg/m^2 which is then followed by the infusion of gemcitabine at a dose of 1000 mg/m^2 [26]. In the

Netherlands, FOLFIRINOX is the standard of care in patients with good performance status (WHO performance state 0–1). In case of disease progression in response to FOLFIRINOX chemotherapy, gemcitabine plus nab-paclitaxel is administered as second-line treatment [23]. In some centers gemcitabine plus nab-paclitaxel is preferred over FOLFIRINOX as first-line treatment as this regimen is broadly better tolerated [27]. However, there is some evidence to suggest that FOLFIRINOX may be superior to gemcitabine nab-paclitaxel as preoperative treatment for BRPC [28].

47.3.2 Side Effects

Most patients who either receive FOLFIRINOX or gemcitabine-nab-paclitaxel.

may experience toxicity. The most common reported complications are fatigue, vomiting, diarrhea, sensory neuropathy, thromboembolism and hematologic changes such as (febrile) neutropenia, thrombocytopenia and anemia. Neutropenia and fatigue are reported in over 20% of patients who receive FOLFIRINOX [20].

In order to prevent nausea, anti emetics are administered routinely with each cycle [20]. In order to prevent neutropenia granulocyte colony stimulating factor (G-CSF) can be administered [26].

47.4 Response and Restaging After Induction Chemotherapy

47.4.1 Radiographic Response

After 2–3 months chemotherapy, contrast-enhanced CT-imaging is generally repeated to determine the response to preoperative chemotherapy. In most centers this is assessed according to the response evaluation criteria in solid tumors (RECIST) [29]. By RECIST definitions, patients are classified as either having progressive disease, stable disease, partial response or complete response. The criteria for each category are summarized in Table 47.2. In addition to CT scan, MRI or ultrasonography may be performed to rule out suspect liver lesions.

It is, however, often difficult to determine radiologic response after preoperative chemotherapy, because CT scan is unable to differentiate between vital tumor and desmoplastic reaction (i.e. fibrosis). As a consequence, resectability is often underestimated. Several experts therefore advise surgical exploration in patients with at least non-progressive disease after preoperative therapy [30]. However, using this approach, a large proportion of patients (30–40%) may undergo futile surgery, which could lead to complications or even mortality [31]. Surgical exploration without resection is previously associated with a doubled risk of 30-day mortality compared with exploration with resection.

Table 47.2 Tumor response scores according to the RECIST 1.1 criteria

Score		Radiographic	Histopathologic
1	Complete response	Loss of all target lesions	No vital tumor cells
2	Partial response	30% decrease of target lesions	Signs of tumor regression
3	Stable disease	No change or minor changes that do not convene to the criteria in score 1 and 2	No change or minor changes that do not convene to the criteria in score 1 and 2
4	Progressive disease	20% increase of target lesions or distant metastasis	Distant metastasis

Better techniques for determination of resectability before exploration are warranted. An intra-operative ultrasound (IOUS) in patients with vascular involvement may be useful, as it may better determine resectability as compared to the preoperative CT scan, however remain intra operative [19].

47.4.2 Biochemical Response

Besides imaging, biomarkers have proven to be valuable in predicting response to preoperative treatment and demonstrate an association with resectability and survival. As stated previously, CA19-9 is currently the only approved biomarker for pancreatic cancer to evaluate response to preoperative chemotherapy. If CA19-9 shows a decrease of more than 30–50%, or normalization, in response to preoperative therapy, it is associated with a higher rate of R0-resection and improved overall survival [15, 16].

Suker et al. also found a significant association with CEA in the prediction of metastatic disease. In case of a CEA ≥5 μg/L there is a risk of 91% for occult metastases, compared with a risk of 4% in patients with a CEA level <5 μg/L [32].

47.4.3 Histopathologic Response

Complete pathologic response (i.e. 0% viable tumor cells in the resection specimen) in response to preoperative chemotherapy is associated with prolonged survival [33]. A retrospective study investigated the effect of chemoradiotherapy in 186 patients with BRPC and LAPC and demonstrated a disease-free survival of 26 months in patients with a complete response compared to 12 months in both patients with a nearly complete response or limited response [34].

Another retrospective study comprising 415 patients with LAPC demonstrated a median overall survival of more than 60 months in the 10% of patients with a

complete pathological response to FOLFIRINOX chemotherapy [35]. In addition, a study showed smaller median tumor size, significantly less lymphatic and perineural invasion and a significant lower number of tumor positive lymph nodes in 40 patients with LAPC and BRPC after preoperative therapy compared with 87 patients who underwent upfront surgery [36]. These findings were confirmed by two randomized controlled trials that compared preoperative chemoradiotherapy followed by surgery with upfront surgery in (borderline) resectable pancreatic cancer [37, 38].

47.5 Outcomes

47.5.1 Borderline Resectable Pancreatic Cancer

Two recently completed randomized-trials from South-Korea and the Netherlands compared preoperative gemcitabine-based chemoradiotherapy with upfront surgery in patients with borderline resectable pancreatic cancer [38, 39]. Although the Dutch PREOPANC trial did not find a significant survival benefit of preoperative chemoradiotherapy (16.0 months vs. 14.3 months, hazard ratio, 0.78; 95% CI, 0.58–1.05; $p = 0.096$) nor a benefit regarding the resection rate (61% vs 72%, $p = 0.058$), these patients did demonstrate superior outcomes with regards to the R0-resection rate (71% vs 40%, $p < 0.001$) and lower rates of pathologic lymph nodes, perineural invasion and venous invasion (Fig. 47.1). Notably, over half of all included patients had primary resectable pancreatic cancer. In the subgroup of patients with borderline resectable pancreatic cancer the survival benefit was significant (17.6 months vs 13.2 months, hazard ratio 0.62; 95% CI 0.40 to 0.95, $p = 0.029$). Furthermore, the rate of R0 resection was six times higher with preoperative chemoradiotherapy (79% vs 13%, odds ratio 24.20; 95% CI 6.57–89.12, $p = 0.001$).

The Korean BorderlinePancreas trial also reported an improved R0-resection rate and a significant survival benefit of preoperative treatment (median overall survival 21 months vs. 12 months, hazard ratio 1.495, 95% confidence interval 0.66–3.36, $p = 0.028$) in patients with BRPC who received preoperative chemoradiotherapy.

These results are in accordance with a previous meta-analysis of 38 studies with nearly 4000 patients which demonstrated a lower resection rate following preoperative treatment (66.0% vs. 81.3%, $p < 0.001$), but a higher proportion of R0-resections (86.8% vs. 66.9%, $p < 0.001$) and improved survival after preoperative treatment (18.8 months vs. 14.8 months) [40]. A recent meta analysis of all six randomized trials comparing preoperative chemoradiotherapy (four trials) or chemotherapy, al gemcitabine based, versus immediate surgery found a significant survival benefit for both borderline and resectable pancreatic cancer [41].

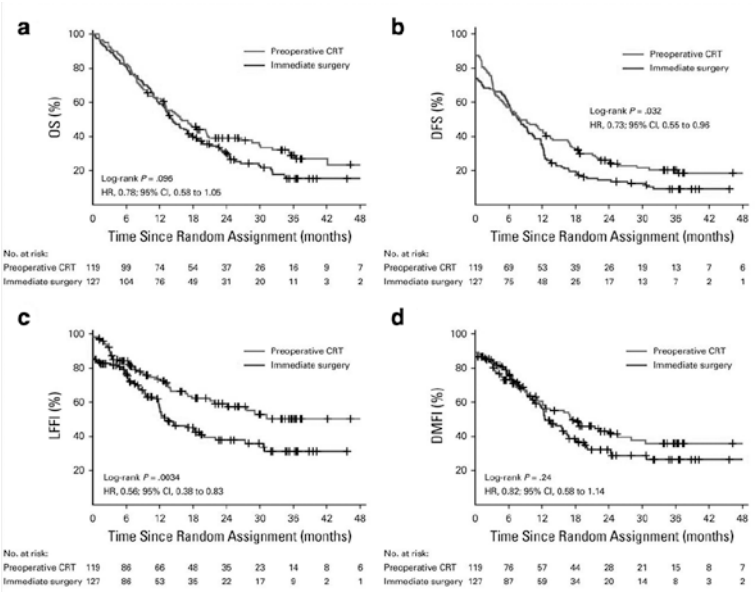

Fig. 47.1 Survival outcomes reported in the PREOPANC trial. (**a**) Overall survival (OS), (**b**) disease-free survival (DFI), (**c**) locoregional failure–free interval (LFFI), and (**d**) distant metastasis–free interval (DMFI) by intention-to-treat analysis in 246 patients randomly assigned to preoperative chemoradiotherapy (CRT; 119 patients) or immediate surgery (127 patients) in the PREOPANC-trial. HR, hazard ratio (Adapted from Versteijne et al. J Clin Oncol 2020 [38])

47.5.2 Locally Advanced Pancreatic Cancer

The implementation of FOLFIRINOX and gemcitabine and nab-paclitaxel appears to have improved the outcomes of patients with LAPC [42]. Whereas Gemcitabine monotherapy for LAPC is associated with a median overall survival of only 6–13 months, a meta-analysis has suggested superior outcomes of FOLFIRINOX in this setting. Moreover, FOLFIRINOX can result in downstaging of LAPC to resectable disease in 28% of the patients. The patient-level meta-analysis by Suker et al. demonstrated a 24.2 months median overall survival in the total group of patients with LAPC receiving FOLFIRINOX, with a pooled resection rate of 25.9% [43].

47.6 Ablation Following Induction Chemotherapy

In patients with LAPC in whom a resection is not feasible following induction chemotherapy, local ablation may be used. The most familiar and investigated ablation techniques are stereotactic body radiation therapy (SBRT), radiofrequency ablation

(RFA), and irreversible electroporation (IRE). The eligibility for local therapy is evaluated by a multidisciplinary team including interventional radiologists, surgeons and radiation oncologists. The decision to perform either technique depends on the orientation of the tumor and it's relation to surrounding vital structures. Besides the local effect, several studies show that these techniques activate a systemic anti-tumor response, so called abscopal effect [44–46].

RFA is based on in the induction of coagulative necrosis due to thermal damage to the tissue [26]. A safety-margin from surrounding healthy tissue from the ablation zone is required to avoid thermal damage, therefore this technique is not eligible for complete tumor ablation (i.e. debulking). One study demonstrated a median overall survival between 19.0 and 25.6 months when RFA is combined with chemotherapy [47]. The PELICAN trial of the Dutch Pancreatic Cancer Group is currently investigating the added value of RFA to preoperative treatment in LAPC in Europe (Netherlands Trial Registry number NTR5517).

SBRT consists of high doses of radiation with a short and accurate delivery which can enhance local control [48]. Petrelli et al. demonstrated an overall survival at 1 year of >50% with a local control rate of >70% in patients with LAPC and BRPC [49]. However, toxicity is an important restricting factor in SBRT. Some studies report side effects that appear in a relatively late phase, especially affecting the gastrointestinal system, such as bleedings and ulceration [49]. To prevent such side effects one should be very accurate in dose gradient at the borders of the target volume [50].

IRE is an upcoming local treatment which is believed to be primarily non-thermal and therefore more feasible and safe with respect to the preservation of surrounding structures [51]. It's mechanism is based on electric pulses which cause nanopore formation based on an alternation in the cell membranes' potential [52]. As a result, tumor cells die due to apoptosis, which also contributes to an abscopal effect [44].

47.7 Conclusion

Patients with LAPC or BRPC remain a challenging group with several recent promising developments. Despite the increased use of FOLFIRINOX and advancements regarding local treatment options including conversion surgery in LAPC, overall prognosis remains poor. Innovative techniques and medication, possible new predictive tools and accurate patient selection are crucial and therefore important issues for further investigation.

References

1. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791):607–20.
2. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB 3rd, Casper ES, et al. Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2012;10(6):703–13.

3. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2018;4(7):963–9.
4. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol. 2014;20(31):10740–51.
5. The Royal College of Pathologists. Dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma; 2017. https://www.rcpath.org/resourceLibrary/g091-pancreasdataset-mar17.html.
6. Kim KS, Kwon J, Kim K, Chie EK. Impact of resection margin distance on survival of pancreatic cancer: a systematic review and meta-analysis. Cancer Res Treat. 2017;49(3):824–33.
7. Michelakos T, Pergolini I, Castillo CF, Honselmann KC, Cai L, Deshpande V, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2019;269(4):733–40.
8. Belli C, Cereda S, Anand S, Reni M. Neoadjuvant therapy in resectable pancreatic cancer: a critical review. Cancer Treat Rev. 2013;39(5):518–24.
9. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
10. Yoo C, Kang J, Kim KP, Lee JL, Ryoo BY, Chang HM, et al. Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen. Oncotarget. 2017;8(28):46337–47.
11. Zhan HX, Xu JW, Wu D, Wu ZY, Wang L, Hu SY, et al. Neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of prospective studies. Cancer Med. 2017;6(6):1201–19.
12. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. Top Magn Reson Imaging. 2007;18(6):421–9.
13. Heinrich S, Goerres GW, Schafer M, Sagmeister M, Bauerfeind P, Pestalozzi BC, et al. Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005;242(2):235–43.
14. Chen YI, Ngamruenphong S, Haito-Chavez Y, Bukhari M, Khashab MA. Single-operator pancreatoscopy with electrohydraulic lithotripsy of large pancreatic duct stones in post-Whipple anatomy. Endoscopy. 2016;48:E280.
15. Boone BA, Steve J, Zenati MS, Hogg ME, Singhi AD, Bartlett DL, et al. Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. Ann Surg Oncol. 2014;21(13):4351–8.
16. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105–19.
17. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
18. Suker M, Nuyttens JJ, Groot Koerkamp B, Eskens F, van Eijck CHJ. FOLFIRINOX and radiotherapy for locally advanced pancreatic cancer: a cohort study. J Surg Oncol. 2018;118(6):1021–6.
19. Ta R, O'Connor DB, Sulistijo A, Chung B, Conlon KC. The role of staging laparoscopy in resectable and borderline resectable pancreatic cancer: a systematic review and meta-analysis. Dig Surg. 2019;36(3):251–60.
20. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
21. Maggino L, Malleo G, Marchegiani G, Viviani E, Nessi C, Ciprani D, et al. Outcomes of primary chemotherapy for borderline resectable and locally advanced pancreatic ductal adenocarcinoma. JAMA Surg. 2019;154(10):932–42.
22. Janssen QP. The (cost)effectiveness of neoadjuvant folfirinox versus neoadjuvant gemcitabine based chemoradiotherapy and adjuvant gemcitabine for (borderline) resectable pancreatic cancer (PREOPANC-2 study); 2019.

23. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
24. Tsujimoto A, Sudo K, Nakamura K, Kita E, Hara R, Takayama W, et al. Gemcitabine plus nab-paclitaxel for locally advanced or borderline resectable pancreatic cancer. Sci Rep. 2019;9(1):16187.
25. Miyasaka Y, Ohtsuka T, Kimura R, Matsuda R, Mori Y, Nakata K, et al. Neoadjuvant chemotherapy with gemcitabine plus nab-paclitaxel for borderline resectable pancreatic cancer potentially improves survival and facilitates surgery. Ann Surg Oncol. 2019;26(5):1528–34.
26. van Veldhuisen E, van den Oord C, Brada LJ, Walma MS, Vogel JA, Wilmink JW, et al. Locally advanced pancreatic cancer: work-up, staging, and local intervention strategies. Cancers (Basel). 2019;11(7):976.
27. Muranaka T, Kuwatani M, Komatsu Y, Sawada K, Nakatsumi H, Kawamoto Y, et al. Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. J Gastrointest Oncol. 2017;8(3):566–71.
28. Dhir M, Zenati MS, Hamad A, Singhi AD, Bahary N, Hogg ME, et al. FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic head adenocarcinoma. Ann Surg Oncol. 2018;25(7):1896–903.
29. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
30. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg. 2016;264(3):457–63.
31. van der Geest LGM, Lemmens V, de Hingh I, van Laarhoven C, Bollen TL, Nio CY, et al. Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. Br J Surg. 2017;104(11):1568–77.
32. Suker M, Koerkamp BG, Coene PP, van der Harst E, Bonsing BA, Vahrmeijer AL, et al. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. Eur J Surg Oncol. 2019;45(10):1906–11.
33. Verbeke C, Haberle L, Lenggenhager D, Esposito I. Pathology assessment of pancreatic cancer following neoadjuvant treatment: time to move on. Pancreatology. 2018;2018:S1424-3903(18)30077-2.
34. He J, Blair AB, Groot VP, Javed AA, Burkhart RA, Gemenetzis G, et al. Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer? Ann Surg. 2018;268(1):1–8.
35. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg. 2019;270(2):340–7.
36. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261(1):12–7.
37. Lee DH, Jang JY, Kang JS, Kim JR, Han Y, Kim E, et al. Recent treatment patterns and survival outcomes in pancreatic cancer according to clinical stage based on single-center large-cohort data. Ann Hepatobiliary Pancreat Surg. 2018;22(4):386–96.
38. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020;38(16):1763–73.
39. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268(2):215–22.
40. Versteijne E, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946–58.

41. Cloyd JM, Heh V, Pawlik TM, Ejaz A, Dillhoff M, Tsung A, et al. Neoadjuvant therapy for resectable and borderline resectable pancreatic cancer: a meta-analysis of randomized controlled trials. J Clin Med. 2020;9(4):1129.
42. Zhang Y, Xu J, Hua J, Liu J, Liang C, Meng Q, et al. Nab-paclitaxel plus gemcitabine as first-line treatment for advanced pancreatic cancer: a systematic review and meta-analysis. J Cancer. 2019;10(18):4420–9.
43. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17(6):801–10.
44. Zhao J, Wen X, Tian L, Li T, Xu C, Wen X, et al. Irreversible electroporation reverses resistance to immune checkpoint blockade in pancreatic cancer. Nat Commun. 2019;10(1):899.
45. Al-Sakere B, Bernat C, Andre F, Connault E, Opolon P, Davalos RV, et al. A study of the immunological response to tumor ablation with irreversible electroporation. Technol Cancer Res Treat. 2007;6(4):301–6.
46. Napoletano C, Taurino F, Biffoni M, De Majo A, Coscarella G, Bellati F, et al. RFA strongly modulates the immune system and anti-tumor immune responses in metastatic liver patients. Int J Oncol. 2008;32(2):481–90.
47. D'Onofrio M, Crosara S, De Robertis R, Butturini G, Salvia R, Paiella S, et al. Percutaneous radiofrequency ablation of unresectable locally advanced pancreatic cancer: preliminary results. Technol Cancer Res Treat. 2017;16(3):285–94.
48. Jung J, Yoon SM, Park JH, Seo DW, Lee SS, Kim MH, et al. Stereotactic body radiation therapy for locally advanced pancreatic cancer. PLoS One. 2019;14(4):e0214970.
49. Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. Int J Radiat Oncol Biol Phys. 2017;97(2):313–22.
50. Brunner TB, Nestle U, Grosu AL, Partridge M. SBRT in pancreatic cancer: what is the therapeutic window? Radiother Oncol. 2015;114(1):109–16.
51. Phillips M, Maor E, Rubinsky B. Nonthermal irreversible electroporation for tissue decellularization. J Biomech Eng. 2010;132(9):091003.
52. Bower M, Sherwood L, Li Y, Martin R. Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. J Surg Oncol. 2011;104(1):22–8.

Chapter 48
The Evolution of Adjuvant Trials in Pancreatic Cancer

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Take Home Messages
- Resection with 6 months adjuvant combination chemotherapy provides the best chance for long term survival.
- There is no role for adjuvant chemoradiation.

Pearls and Pitfalls
- Local recurrence occurs a little later than metastatic disease but is not associated with a better overall survival.
- R1-direct margin is associated with local recurrence and is associated with overall survival.
- Local recurrence cannot be used as a surrogate marker for improved overall survival.
- Lung metastasis is associated with longer survival than local recurrence or liver metastasis.

Future Perspectives
- Identifying which patients are more likely to respond to FOLFIRINOX or gemcitabine-capecitabine as first line chemotherapy.
- Association of chemotherapy responsiveness to molecular subtyping.

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48.1 Introduction

Pancreatic cancer is one of the most lethal cancers and is predicted to become the second most common cause of cancer related deaths in the United States by 2030 [1]. There has been only very modest improvement in overall 5 year survival for all stages increasing from under 4% to around 9% in the past decade [2, 3]. The genetic characteristics of pancreatic cancer are now well characterized with distinct high frequency of KRAS, TP53, CDKN2A, and SMAD4 mutations and/or loss of heterozygosity, along with molecular subtyping into classical and basal categories [4–9]. Despite an increasing use of next generation sequencing based on these scientific advances only a minority of assay results lead to a change in clinical management with limited clinical efficacy, with the exception of the uncommon situations in patients with NRG1-fusions in KRAS wild-type tumors and patients with germline BRCA-mutated metastatic pancreatic cancer [10–13]. There is however increasing success using combinations of chemotherapy in the advanced setting [3, 14–17]. Despite remarkable improvement of surgical techniques, surgery by itself only provides relatively little extension of life expectancy with a 5-year survival rate of only 8% or less with resectable disease [17, 18].

48.2 Adjuvant Therapy Trials in Pancreatic Cancer

The groundbreaking studies of the European Study Group of Pancreatic Surgery (ESPAC) transformed our understanding of adjuvant chemotherapy in pancreatic cancer, prompting the development of further types of chemotherapy and also more advanced techniques in surgery and the evolution of neoadjuvant therapy [3, 17–23]. Table 48.1 provides an overview of trials investigating adjuvant therapy after primary resection [18–40].

The *ESPAC-1* trial, a multicenter randomized controlled trial of 545 patients utilized a two-by-two factorial design in 289 patients, randomizing each patient twice to either 5-fluorouracil (5-FU) with folinic acid for 6 months versus observation, or chemoradiotherapy (20 with 5-FU radiosensitization) versus observation, plus additionally another 256 patients into a single randomization, comprising 68 patients randomly assigned to chemoradiotherapy or no chemoradiotherapy and 188 to chemotherapy or no chemotherapy [18]. Early publication was recommended because of the lack of evidence to support the use of adjuvant chemoradiation after a median follow-up of 10 months, with a median survival of 15.5 months in 175 patients with chemoradiotherapy versus 16.1 months in 178 patients without chemoradiotherapy. There was evidence of a significant survival benefit for adjuvant chemotherapy with a median survival of 19.7 months in 238 patients with chemotherapy versus 14.0 months in 235 patients without chemotherapy [18]. With mature follow-up 47 months in the pure 2 × 2 factorial design section the estimated 5-year survival rate was 10% among patients assigned to receive chemoradiotherapy and 20%

Table 48.1 Randomized clinical trials investigating the effect of adjuvant treatment following surgical resection

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
Adjuvant trials							
GITSG 9173	Kalser et Ellenberg [24, 25]	1974–1982	CRT + 5FU	21	21.0	19	All R0
			Observation	22	10.9	5	
					P = 0.03		
Norway multi-center	Bakkevold et al. [26]	1984–1987	5-FU/DOX/MMC	30	23	4	Included 14 patients with adenocarcinoma of the ampulla
			Observation	31	11	8	
					P = 0.04		
Japan multi-center	Takada et al. [27]	1986–1992	MMC/Oral 5-FU	81	17.1	11.5	Included patients with metastases MMC/Oral 5-FU: Curative resection in 45 Observation: Curative resection in 47 Not significant
			Observation	77	12.6	18	
EORTC 40891	Klinkenbijl et al. [28] Smeenk et al. [29]	1987–1995	CRT	60	24.5	20	T1–2, N0–1a, M0 pancreatic head cancer. Not significant
			Observation	54	19.0	10	
					P = 0.099		
ESPAC-1 (all patients and early follow-up of 2 × 2 factorial patients)	Neoptolemos et al. [18]	1994–2000	No CRT	178	16.1	19.5	ECOG 0,1,2
			CRT	175	15.5	10.3	R0/R1
				P = 0.24			Significant for chemotherapy overall but not in the 2 × 2 factorial. Not significant for CRT overall or in 2 × 2 factorial
			No chemotherapy	235	14.0	9.9	
			5FU/FA	238	19.7	23.3	
				P = 0.0005			

(continued)

Table 48.1 (continued)

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
ESPAC-1 (2 × 2 only)	Neoptolemos et al. [19]	1994–2000	No CRT	144	17.9	19.6	ECOG 0,1,2 R0/R1 2 × 2 factorial design: each patient randomized twice to chemotherapy with 5FU/FA or no chemotherapy and CRT vs. no CRT. Significant for chemotherapy in the 2 × 2 factorial with additional target events. Not significant for CRT
			CRT	145	15.9	10.8	
					P = 0.05		
			No chemotherapy	142	15.5	8.4	
			5FU/FA	147	20.1	21.1	
					P = 0.009		
			Observation	69	16.9	10.7	
			CRT	73	13.9	7.3	
			5FU/FA	75	21.6	29.0	
			CRT + 5FU/FA	72	19.9	13.2	
CONKO-001	Oettle et al. [30, 31]	1998–2004	GEM	179	22.1	22.5	Postoperative CA19-9 > 92.5 kU/L = 0.0%
			Observation	175	20.2	11.5	
					P = 0.01		
JSAP-02	Ueno et al. [32]	2002–2005	GEM + IORT in 27	58	22.3	23.9	Karnofsky >50 Not significant
			IORT in 47 then observation	60	18.4	10.6	
					P = 0.19		

RTOG 9704	Regine et al. [33, 34]	1998–2002	5-FU/FA, followed by 5-FU-based CRT, followed by 5-FU/FA	230	–	–	538 patients recruited but then 87 patients were excluded at analysis for being ineligible. Overall results of 451 'eligible' patients were not reported. 388 had pancreatic head tumors with a median survival of 20.5 months and a 3-year survival of 31% in the GEM group vs. 16.9 months and 22% in the 5-FU group (HR, 0.82 [95% CI, 0.65–1.03]; P = 0.09) Not significant
			GEM, followed by 5-FU-based CRT, followed by GEM	231	–	–	
					P = 0.34		
ESPAC-3	Neoptolemos et al. [21]	2000–2007	5-FU/FA	221	23.0	15.9	ECOG 0, 1, 2 R0/R1 Not significant
			GEM		23.6	17.5	
					P = 0.39		
CapRI	Schmidt et al. [35]	2004–2007	5-FU, + cisplatin + IFN-α2b with radiotherapy, then continuous 5-FU infusion	64	32.1	25	ECOG 0, 1, 2 R0/R1 Not significant
			5-FU/FA	68	25.5	25	
					P = 0.49		
JASPAC-01	Uesaka et al. [36]	2007–2010	GEM	190	25.5	24.4	ECOG 0,1 Postoperative CA19-9 > 37 kU/L = 21% R1 positive = 31% Lymph node positive = 62.9% WHO 0 = 68.7%.
			S-1	187	46.5	44.1	
					P < 0.0001		

(continued)

Table 48.1 (continued)

Trial	Reference	Recruitment period	Treatment arms	Number of patients	Median overall survival (months)	5-year overall survival (%)	Comments
CONKO-005	Sinn et al. [37]	2008–2013	GEM	217	26.2	20.0	Karnofsky PS ≥ 60% Only R0 resected patients.
			GEM erlotinib	219	24.5	25.0	
					P = 0.061		
CONKO-006	Sinn et al. [38]	2008–2013	GEM	65	17.1	–	Karnofsky PS ≥ 60% Only R1 patients
			GEM + sorafenib	57	18.2	–	
					P = 0.94		
ESPAC-4	Neoptolemos et al. [23]	2008–2014	GEM	366	25.5	16.3	R0 and R1 patients
			GEM + capecitabine	365	28.0	28.8	
					P = 0.032		
PRODIGE-24	Conroy et al. [39]	2012–2016	GEM	246	35.0	–	R0 and R1 patients ECOG PS 0/1 Post-OP CA 19-9 < 180 KU/L <80 years
			mFOLFIRINOX	247	54.4	–	
					P = 0.003		
APACT	Tempero et al., 2019 [40]	2014–2018	GEM	866 randomized 1:1	36.2		R0 and R1 patients ECOG PS 0/1 Post-OP CA 19-9 < 100 KU/L Primary endpoint = DFS Independent reviewer DFS: • 18.0 months—GEM • 19.4 months—GEM + NabP P = 0.1824 Primary endpoint not met FDA did not approve indication for adjuvant Gem-NabP in PDAC
			GEM + Nab-P		40.5		
					Interim analysis Nominal P = 0.045		

Prep-02/ JSAP-05 Japan, multi-center	Unno et al. 2019 [41]	2013–2016	GEM+S1 + surgery + S1 Upfront resection + S1	82 (not resected = 42)	36.7	–	ECOG = 0,1. Age < 80 years. Neo-adjuvant gemcitabine and S1 for two cycles. Both arms adjuvant S1 for 6 months. Referred to as a trial in resectable pancreatic cancer but not all were resected. In the JASPAC-01 trial the median survival in the S1 adjuvant group was 44.1 months
				180 (not resected = 51)	26.6		
				1	P = 0.015		

CRT chemoradiotherapy, *5-FU* 5-fluorouracil, *DOX* doxorubicin, *MMC* mitomycin C, *FA* folinic acid, *GEM* gemcitabine, *IORT* intra-operative radiotherapy, *mFOLFIRINOX* modified folinic acid, 5-fluorouracil (5-FU), irinotecan and oxaliplatin, *Nab*-P nab-paclitaxel

among patients who did not receive chemoradiotherapy, 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy [19]. The survival benefit of chemotherapy persisted after adjustment for major prognostic factors [19].

The Charité Onkologie *(CONKO)-001* trial randomized 186 patients to adjuvant gemcitabine for 6 months and 182 to observation. Disease free survival, the primary end-point with a median follow-up of 53 months was 13.4 months in the gemcitabine group, significantly longer than the 6.7 months in the observation group. There was no significant difference in median overall survival between the gemcitabine group with 22.1 months versus 20.2 months in the observation group, nor in 5-year survival at 22.5% and 11.5% respectively [30]. At subsequent median follow-up time of 136 months, the 5-year overall survival of 20.7% in the gemcitabine and 10.4% was statistically significant [31].

The *ESPAC-3v2* trial (2000–2007) showed gemcitabine not to be superior to 5-FU with a median overall survival rate of 23.6 months versus 23.0 months but with less cumulative toxicity [21]. Furthermore, additional analysis of the *ESPAC-3* data was able to show that the completion of 6 cycles of chemotherapy, but not early initiation was associated with improvement in overall survival [22]. Presumably, because without full recovery from surgery, the completion of the recommended number of chemotherapy cycles is less likely because of accumulating fatigue and therefore insufficient to treat occult systemic disease. Combining the control arms from ESPAC1 and ESPAC3v2 also established that adjuvant 5-FU with folinic acid was superior to observation [22].

The combination of gemcitabine and capecitabine has been shown to be an effective regimen in the advanced setting [12]. The *ESPAC-4* trial included 730 patients, 366 of which were randomly assigned to gemcitabine, and 364 to gemcitabine and capecitabine. Patients eligible had to be >18 years of age and needed to have an R0 or R1 resection, but there were no other major exclusion criteria such as low carbohydrate antigen (CA)19-9 levels [23]. The median overall survival was 28.0 (95% CI = 23.5–31.5) months in the gemcitabine and capecitabine group versus 25.5 (95% CI 22.7–27.9) months in the gemcitabine group. The number of grade 3–4 adverse events was similar in both groups [23]. The substantive improvement survival of single agent chemotherapy and then doublet chemotherapy compared to chemoradiotherapy or no adjuvant therapy is shown in Fig. 48.1 and Table 48.2.

The *JSAP-05 trial* randomized 182 patients to neoadjuvant chemotherapy with S-1 plus gemcitabine and 180 patients to upfront surgery in resectable and borderline pancreatic cancer followed by 6 months adjuvant chemotherapy with S-1 [41]. In the neoadjuvant group 140 (76.9%) were resected compared to 129 (71.6%) in the upfront surgery group. What remains unexplained is that the adjuvant S-1 arm had a median survival of only 26.6 months, since the *JASPAC-01* trial showed a median overall survival of 46.5 months in patients randomized to adjuvant S-1 [36].

In 2011, a new therapy regimen based containing oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) was introduced in patients with metastatic pancreatic cancer [13]. An improved survival in the FOLFIRINOX group in

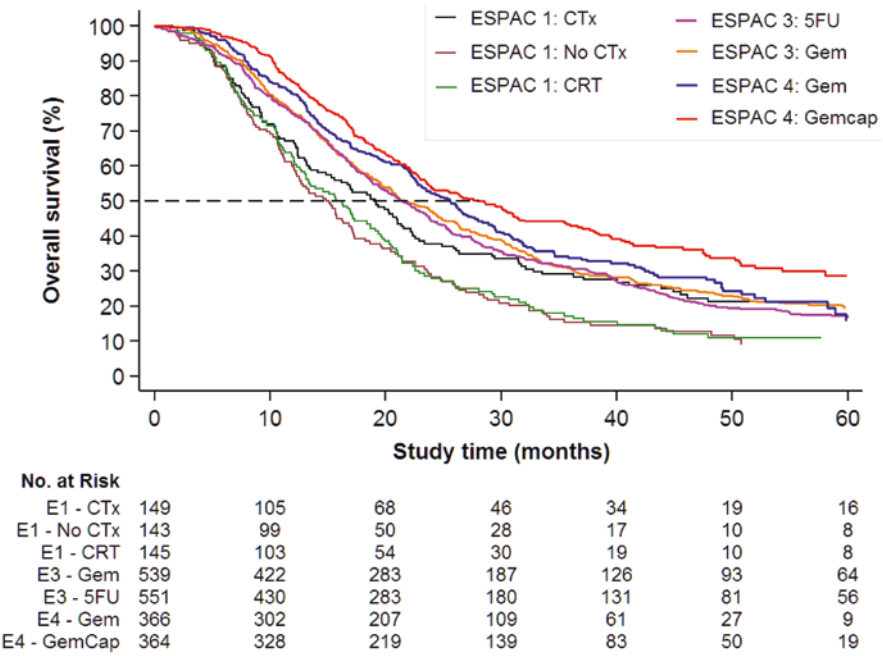


Fig. 48.1 Kaplan Meier survival estimates in the ESPAC trials (From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix)

relatively fit patients with metastatic disease was observed compared to gemcitabine, however the more aggressive scheme of FOLFIRINOX was associated with significantly higher rates of grade 3–4 toxicity events and reduced quality of life [42]. To reduce side-effects, modified versions of FOLFIRINOX (mFOLFIRINOX), e.g. without the 5-fluorouracil bolus, with lower irinotecan dose or obligatory hematopoietic growth factor Pegfilgrastim have been described [43]. In a retrospective review of 60 patients with metastatic pancreatic cancer, a modified FOLFIRINOX had similar efficacy in metastatic disease while reducing toxicity and improving safety profiles [43].

The French-Canadian *PRODIGE* [Partenariat de Recherche en Oncologie Digestive] *24-ACCORD* [Actions Concertées dans les Cancers Colorectaux et Digestifs] *24* and *CCTG PA.6* [Canadian Cancer Trials Group Pancreatic Adnocarcinoma] trial showed that in a selected group of macroscopically resected patients the estimated 5-year survival rate could be pushed towards 50% with a modified FOLFIRINOX regimen—the best 5-year survival ever reported. The investigators randomized 493 patients to receive either mFOLFIRINOX or gemcitabine for 24 weeks. Patients with CA19-9 > 180 U/ml within 21 days before randomization and WHO performance status of >1 were not eligible for randomization. Median survival reached 54.4 months in the mFOLFIRINOX group compared to 35 months in the gemcitabine group. Interestingly, while the median

Table 48.2 Five year overall survival rates in the ESPAC trials

Trial		Treatment	Number of patients (total = 2092)	5-Year overall survival (95% confidence interval)	Stratified log-rank χ^2	*P*-value
ESPAC-1	Neoptolemos et al. [18] Neoptolemos et al. [19]	5-fluorouracil/ folinic acid	149	21 (14.6–28.5) %	7.03	0.030[a]
		No chemotherapy	143	8.0 (3.8–14.1) %		
		Chemoradiotherapy (5-fluorouracil Radiotherapy)	145	10.8 (6.1–17.0) %		
ESPAC-3	Neoptolemos et al. [21]	Gemcitabine	539	17.5 (14.0–21.2) %	0.74	0.390[a]
		5-fluorouracil/ folinic acid	551	15.9 (12.7–19.4) %		
ESPAC-4	Neoptolemos et al. [23]	Gemcitabine	366	16.3 (10.2–23.7) %	4.61	0.032[b]
		Gemcitabine and capecitabine	364	28.8 (22.9–35.2) %		

From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix
[a]Stratification factor: resection margin status
[b]Stratification factors: resection margin status and country

disease free survival in the gemcitabine group was similar to the previous trials, median overall survival was longer, potentially pointing to the selected patient population or frequent use of mFOLFIRINOX in patients showing relapse [39]. It should be noted that mFOLFIRINOX is suitable only for relatively fit patients applicable to around 30–40%, the remainder needing to be given gemcitabine and capecitabine.

In patients with metastatic pancreatic cancer increased survival has also been shown with nanoalbumin-bound (nab)-paclitaxel plus gemcitabine [14]. The *APACT study* assessed effects of nab-paclitaxel and gemcitabine versus gemcitabine monotherapy in surgically resected pancreatic cancer patients. Exclusion criteria were CA19-9 levels ≥100 U/ml and ECOG performance status ≥1, with a primary end-point of disease-free survival. There were 866 patients randomized with median disease-free survival of 19.4 months in the nab-paclitaxel and gemcitabine group, not significantly different from 18.8 months in the gemcitabine group, hazard ratio of 0.88, 95% CI = 0.729–1.063 (P = 0.1824) [40]. As the primary end-point was not met the use of nab-paclitaxel as adjuvant treatment in pancreatic cancer is not approved by the Federal Drugs Administration.

48.3 Adjuvant Chemoradiotherapy Trials in Pancreatic Cancer

Adjuvant chemoradiation is still used in some countries, especially the USA, and the National Comprehensive Cancer Network guideline lists adjuvant chemoradiation as an option, although no evidence level for this recommendation is provided [44]. European and UK guidelines do not support the use of adjuvant chemoradiation for pancreatic cancer [45, 46]. Previous studies such as the *EORTC 40891* (1987–1995), *ESPAC-1* (1994–2000), and *RTOG 9704* (1998–2002) trials failed to show improved survival using adjuvant radiotherapy and or chemoradiation either with or without additional chemotherapy [18, 19, 28, 29, 33, 34]. The Gastro-Intestinal Study Group *(GITSG) trial 9173* randomized 43 patients to split-course radiotherapy with radiosensitising 5-FU and maintenance systemic weekly 5-FU after surgery or surgery alone. There was a survival benefit for adjuvant treatment, with a median survival of 20 versus 11 months and a 2-year survival of 42% vs. 15%, respectively [24]. A further 30 patients were added to the adjuvant therapy arm, and the outcome became modified to a median survival of 18 months and a 2-year survival of 46% [25]. The GITSG trial only included negative resection margins, thereby preselecting a prognostically favorable group. A Phase III multicenter trial by the European Organization for Research and Treatment of Cancer trial (EORTC) randomized 218 patients with T1-2,N0-1a, M0 pancreatic ductal adenocarcinoma and T1-3, N0-1a, M0 periampullary adenocarcinoma, either to adjuvant chemoradiotherapy as in the GITSG trial but without maintenance chemotherapy, or to observation [28, 29]. There were 114 patients with pancreatic ductal carcinoma, of whom 60 were randomized to treatment and 54 to observation with median survivals of 17.1 and 12.6 months, respectively [28]. This difference was not statistically significant (P = 0.09) [28]. After a median follow-up of 11.7 years, 173 deaths (79%) were then reported but with the overall survival still did not differ sufficiently between the chemoradiation treatment versus the control groups confirming the previous short-term analysis, indicating no benefit of adjuvant chemoradiation over observation in patients with resected pancreatic cancer or periampullary cancer [29]. The ESPAC 1 trial also reported no significant difference in survival between patients randomized to chemoradiotherapy (as in the GITSG trial), with a median of 15.5 months versus 16.1 months for patients randomized to no chemoradiotherapy (P = 0.24) [18]. The *RTOG 0848 trial*, a large randomized phase III study with 952 patients that investigates the value of additional chemoradiation for patients with no progression after standard adjuvant chemotherapy with gemcitabine is currently ongoing.

Radiotherapists from the USA especially have been critical of the ESPAC trials whilst promoting non-significant findings such as those from the RTOG 9704 adjuvant chemoradiation trial [33, 34, 47]. In the *RTOG 9704* trial there was no significant difference in survival between patients randomized to chemoradiation plus fluorouracil and those randomized to chemoradiation plus gemcitabine with a median overall survival of around 16 months, identical to that of patients who

received chemoradiation in the ESPAC-1 trial [18, 19]. This was after exclusion of 87 of the 531 patients that had already been randomized in RTOG 9704 to ensure that all of those eventually analyzed had adhered to the protocol. In comparison, patients randomized in the ESPAC-1, ESPAC-3 and ESPAC-4 trials to single agent chemotherapy (either 5-fuorouracil or gemcitabine) had survival rates of 21–26 months with 5 year survival rates of 16–18% based on intention to treat analysis (even if reduced doses or no adjuvant therapy was received) and a median survival rates of 28 months with 5 year survival rates of and 29% respectively in those randomized to gemcitabine and capecitabine [18, 19, 21, 23]. No randomized adjuvant chemoradiation trial has even got close to matching these survival data. In experimental studies the pancreata of genetically engineered KC mice exposed to radiation had significantly more advanced pancreatic intraepithelial lesions and more invasive cancer foci than pancreata of control mice, and as a corollary radiation exposure reduced median survival by more than 6 months [48]. Radiotherapists have been criticised in an editorial in the Journal of the National Cancer Institute for "few good data, much debate" [49]. A network meta-analysis from 2013 for adjuvant treatments for resected pancreatic cancer by Liao et al. concluded that chemotherapy with fluorouracil or gemcitabine was the optimum adjuvant treatment for pancreatic cancer and reduced mortality after surgery by about a third whilst chemoradiation plus chemotherapy was less effective in prolonging survival and was more toxic than chemotherapy alone [50].

48.4 Local/Distant Recurrence

A secondary analysis of ESPAC-3 has demonstrated that resection margin (R) involvement, specifically R1-direct tumor margins, poor tumor differentiation, positive lymph node status, WHO performance status ≥1, maximum tumor size, and an R1-direct posterior resection margin were all independently significantly associated with reduced overall and recurrence-free survival [51]. Moreover, overall R1-direct positive resection margin status, positive lymph node status, WHO performance status ≥1, and R1-direct positive superior mesenteric/medial margin resection status were all significantly associated with local recurrence [51].

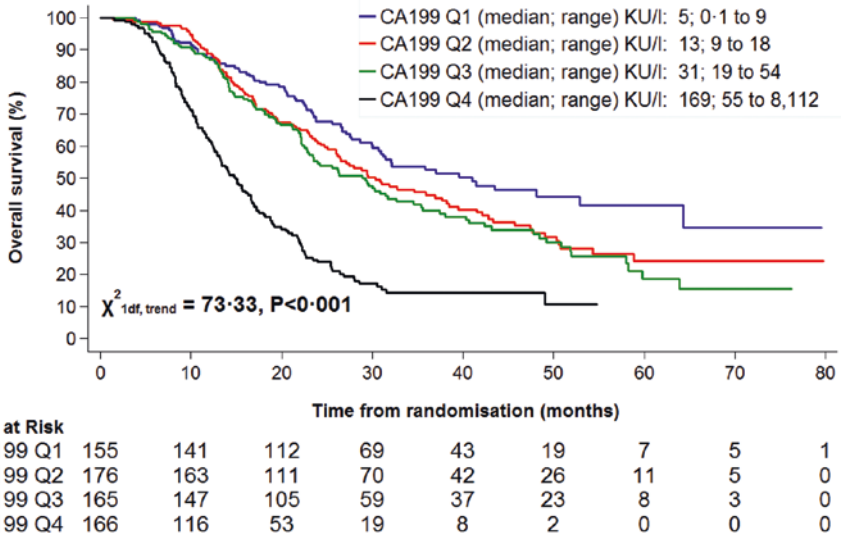
A further secondary analysis of ESPAC-4 demonstrated that there were no significant differences between the time to recurrence and subsequent and overall survival between local and distant recurrence [52]. The median overall survival of patients with distant-only recurrence (23.0 months) or local with distant recurrence (23.8 months) was not significantly different from those with only local recurrence (24.8 months). Patients with metastases to the lungs had a much longer survival compared to those with local recurrence or metastases to other sites such as the liver. Gemcitabine plus capecitabine had a 21% reduction of death following recurrence compared with monotherapy. Thus, pancreatic cancer appears to behave as a *systemic disease* requiring effective systemic therapy after resection [53].

These studies show that a positive resection margin is associated with a reduction in overall survival, for example in the ESPAC-4 trial a reduction in 5-year survival from 40% to 20% [23]. Whilst a positive resection margin is also associated with an increased likelihood of local recurrence, this of itself is not the contributor to reduced survival, but rather reflects the increased likelihood of systemic disease [51, 52]. Thus, strategies aimed at local control, may reduce subsequent local progression, but will not improve overall survival.

48.5 Prognostic Factors

It is very important to be aware of key prognostic factors when comparing survival outcomes from different trials and differing therapeutic regimens as this will have a powerful effect on survival outcomes. Multivariate analysis of 17 prospectively determined clinical, biochemical, pathological and treatment factors in the ESPAC-4 trial, identified the following as independent prognostic risk factors: gemcitabine plus capecitabine treatment, R1 resection margin, postoperative CA19-9 levels, moderately well differentiated tumors, poorly differentiated tumors, undifferentiated tumors, positive lymph nodes, and maximum tumor size [23]. In a single center cohort study from the Nanjing University Pancreas Center comprising 432 patients who had resected pancreatic cancer (2009–2014), the independent predictive factors for overall survival also included adjuvant chemotherapy along with the preoperative neutrophil-lymphocyte ratio and CA19-9 levels, tumor differentiation, tumor stage, lymph node ratio, microscopic nerve and vascular invasion and the presence of metastases [53].

Unlike a number of other trials, the ESPAC trials did not have restrictive criteria which otherwise are liable to produce favorable outcomes. Figure 48.2 illustrates survival by postoperative CA19-9 levels in the ESPAC-4 trial [23]. The CONKO-001 trial excluded patients with postoperative CA19-9 levels >92.5 KU/L [30]. Exclusion of patients in the ESPAC-4 trial by postoperative CA19-9 levels >92.5 KU/L would directly result in improved survival rates in both arms of the trial [23]. The APACT trial also restricted patients to the trial with postoperative CA19-9 levels <100 KU/L leading to apparently favorable survival rates [40]. Clear resection margin R0 rates were 83% in CONKO-001, 87% in JASPAC-01, and 76.3% in APACT [30, 36, 40]. The PRODIGE-24/CCTAG-PA6 trial had 57.2% R0 resections with the effect for mFOLFIRINOX being strongest for R1 resections [39]. On the other hand, ESPAC-4 had only 40% R0 resections and with a 5-year survival estimate in R0 patients of 40% in patients given gemcitabine plus capecitabine [23]. Lymph node clear N0 was present in 28.2% of patients in CONKO-001, 37.1% in JASPAC-01, 25.5% in the PRODIGE-24/CCTAG-PA6 trial, and 28.7% in APACT. In the ESPAC-4 trial only 19.6% of patients had an N0 resection but in these the 5-year survival rate nearly reached 50% [23]. Restrictive selection criteria will also result in a higher proportion of patients with a normal postoperative CA19-9 level, even if this was



No. at Risk									
CA199 Q1	155	141	112	69	43	19	7	5	1
CA199 Q2	176	163	111	70	42	26	11	5	0
CA199 Q3	165	147	105	59	37	23	8	3	0
CA199 Q4	166	116	53	19	8	2	0	0	0

Fig. 48.2 Kaplan Meier survival estimates for postoperative carbohydrate antigen (CA)19-9 levels by quartile (25%) levels, 1–4 (Q1, Q2, Q3, and Q4) in the ESPAC4 trial (From Neoptolemos JP, et al. Lancet. 2017;389(10073):1011–24. Supplementary appendix)

not a specific selection criterion, for example, this was found in 77% of patients in the JASPAC-01 trial [36]. In APACT 80.4% had a postoperative CA19-9 level <37 KU/L [40].

48.6 Conclusion

Significant progress in the treatment of pancreatic cancer has been made in the last 20 years [3, 17, 54]. A major impact has been the dramatic improvements in surgical technique, management of post-operative complications facilitated by the centralization of pancreatic cancer surgery [17, 54–56]. The development of international guidelines for the definition of surgical techniques and postoperative complications for pancreatic cancer has been essential for objective assessment of outcomes helping to drive technical progress. This has been most noticeably from the *International Study Group on Pancreatic Surgery* that includes definitions on the extent of pancreatectomy and lymphadenectomy, the pancreatic anastomosis and post-operative complications including pancreatic fistula, hemorrhage, and delayed gastric emptying [57–67]. The impact of next generation sequencing to improve survival by targeted therapy has so far proved to be rather limited [3, 10–13, 17]. The major impact on improvement on survival by systemic therapies has come from chemotherapy [3, 17, 68]. This approach may offer further opportunities to improve survival even more by the use patient-derived tumor organoids from pancreatic cancer as preclinical models to predict response to chemotherapy [69].

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Neoptolemos JP, Kleeff J, Michl P, Costello E, Greenhalf W, Palmer DH. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat Rev Gastroenterol Hepatol. 2018;15(6):333–48.
4. Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321(5897):1801–6.
5. Collisson EA, Sadanandam A, Olson P, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med. 2011;17:500–3.
6. Moffitt RA, Marayati R, Flate EL, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015;47:1168–78.
7. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature 2016;531(7592):47–52.
8. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518(7540):495–501.
9. Connor AA, Denroche RE, Jang GH, Timms L, Kalimuthu SN, Selander I, et al. Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma. JAMA Oncol. 2017;3:774–83.
10. Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. Clin Cancer Res. 2018;24(6):1344–54.
11. Davis W, Makar G, Mehta P, Zhu GG, Somer R, Morrison J, Kubicek GJ. Next-generation sequencing in 305 consecutive patients: clinical outcomes and management changes. J Oncol Pract. 2019;15(12):e1028–34.
12. Heining C, Horak P, Uhrig S, Codo PL, Klink B, Hutter B, et al. NRG1 fusions in KRAS wild-type pancreatic cancer. Cancer Discov. 2018;pii:CD-18-0036. https://doi.org/10.1158/2159-8290.CD-18-0036.
13. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381(4):317–27.
14. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009;27(33):5513–8.
15. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
16. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
17. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
18. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358(9293):1576–85.
19. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
20. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009;100(2):246–50.

21. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
22. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32(6):504–12.
23. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
24. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg (Chicago, Ill 1960). 1985;120(8):899–903.
25. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer. 1987;59(12):2006–10.
26. Bakkevold KE, Arnesjo B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. E J Cancer (Oxford, England: 1990). 1993;29(5):698–703.
27. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002;95(8):1685–95.
28. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82; discussion 82–4.
29. Smeenk HG, van Eijck CH, Hop WC, Erdmann J, Tran KC, Debois M, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg. 2007;246(5):734–40.
30. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
31. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
32. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009;101(6):908–15.
33. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299(9):1019–26.
34. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.
35. Schmidt J, Abel U, Debus J, Harig S, Hoffmann K, Herrmann T, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol. 2012;30(33):4077–83.
36. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3,

open-label, randomised, non-inferiority trial (JASPAC 01). Lancet (London, England). 2016;388(10041):248–57.
37. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: adjuvant chemotherapy with gemcitabine plus erlotinib versus gemcitabine alone in patients after R0 resection of pancreatic cancer: a multicenter randomized phase III trial. J Clin Oncol. 2017;35(29):3330–7.
38. Sinn M, Liersch T, Gellert K, Riess H, Stübs P, Waldschmidt DT, et al. CONKO-006: a randomized double-blinded phase IIB-study of adjuvant therapy with gemcitabine + sorafenib/placebo for patients with R1-resection of pancreatic cancer. Ann Oncol. 2014;25(Suppl 4):mdu438.18-mdu.18. LBA18.
39. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
40. Tempero MA, Reni M, Riess H, Pelzer U, O'Reilly EM, Winter JM, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol. 2019;37(15 Suppl):4000–40.
41. Unno M, Motoi F, Matsuyama Y, Satoi S, Matsumoto I, Aosasa S, et al. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). J Clin Oncol. 2019;37(4 Suppl):189.
42. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23–9.
43. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas. 2013;42(8):1311–5.
44. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw.
45. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
46. O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: a summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology. 2018;18(8):962–70.
47. Boyle J, Czito B, Willett C, Palta M. Adjuvant radiation therapy for pancreatic cancer: a review of the old and the new. J Gastrointest Oncol. 2015;6(4):436–44.
48. Seifert L, Werba G, Tiwari S, Giao Ly NN, Nguy S, et al. Radiation therapy induces macrophages to suppress T-cell responses against pancreatic tumors in mice. Gastroenterology. 2016;150(7):1659–72.
49. Twombly R. Adjuvant chemoradiation for pancreatic cancer: few good data, much debate. J Natl Cancer Inst. 2008;100(23):1670–1.
50. Liao WC, Chien KL, Lin YL, Wu MS, Lin JT, Wang HP, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Lancet Oncol. 2013;14(11):1095–103.
51. Ghaneh P, Kleeff J, Halloran CM, Raraty M, Jackson R, Melling J, et al. The impact of positive resection margins on survival and recurrence following resection and adjuvant chemotherapy for pancreatic ductal adenocarcinoma. Ann Surg. 2019;269(3):520–9.
52. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019; https://doi.org/10.1001/jamasurg.2019.3337.

53. Xu D, Zhang K, Li M, Neoptolemos JP, Wu J, Gao W, Wu P, et al. Prognostic nomogram for resected pancreatic adenocarcinoma: a TRIPOD-compliant retrospective long-term survival analysis. World J Surg. 2020; https://doi.org/10.1007/s00268-019-05325-z.
54. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2019;16(1):11–26.
55. Klaiber U, Roth S, Hackert T, Neoptolemos JP. Evolution of oncosurgical management of pancreatic cancer. Eur Surg. 2019;51(3):165–73.
56. Schneider M, Strobel O, Hackert T, Büchler MW. Pancreatic resection for cancer-the Heidelberg technique. Langenbeck's Arch Surg. 2019;404(8):1017–22.
57. Bassi C, Butturini G, Fingerhut A, Yeo C, Izibicki J, Neoptolemos JP, et al. for the International Study Group on Pancreatic Fistula Definition. Post-operative pancreatic fistula: an International Study Group (ISGPF) definition. Surgery. 2005;138(1):8–13.
58. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying after pancreatic surgery – a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761–8.
59. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Postpancreatectomy hemorrhage (PPH) – an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20–5.
60. Shukla PJ, Barreto SG, Fingerhut A, Bassi C, Büchler MW, Dervenis C, et al. Toward improving uniformity and standardization in the reporting of pancreatic anastomoses: a new classification system by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2010;147(1):144–53.
61. Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M. et al; International Study Group of Pancreatic Surgery. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. Surgery. 2014;155(5):887–92.
62. Hartwig W, Vollmer CM, Fingerhut A, Yeo CJ, Neoptolemos JP, Adham M. et al; International Study Group on Pancreatic Surgery. Extended pancreatectomy in pancreatic ductal adenocarcinoma: Definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). Surgery. 2014;156(1):1–14.
63. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA. et al; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88.
64. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, Andrén-Sandberg A, Asbun HJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fingerhut A, Friess H, Hartwig W, Izbicki JR, Lillemoe KD, Milicevic MN, Neoptolemos JP, Shrikhande SV, Vollmer CM, Yeo CJ, Charnley RM, International Study Group on Pancreatic Surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
65. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adam M. et al; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584–91.
66. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. International Study Group of Pancreatic Surgery (ISGPS). Pancreatic anastomosis after pancreatoduodenectomy. A position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161(5):1221–34.
67. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. International Study Group on Pancreatic Surgery. Definition and classification of chyle leak after pancreatic

operation: a consensus statement by the International Study Group on Pancreatic. Surgery. 2017;161(2):365–72.
68. Springfeld C, Jäger D, Büchler MW, Strobel O, Hackert T, Palmer DH, Neoptolemos JP. Chemotherapy for pancreatic cancer. Presse Med. 2019;48(3 Pt 2):e159–74.
69. Tiriac H, Belleau P, Engle DD, Plenker D, Deschenes A, Somerville TDD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. Cancer Discov. 2018;8(9):1112–29.

Part VII
Surgery

Chapter 49
IPMN as a Premalignant Condition

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Take Home Messages

- The current management of IPMNs is based on guidelines that relies on expert opinions or studies providing low quality evidence.
- While MD-IPMN and MT-IPMN represent an indication for surgery considering the risk of malignancy, the majority of BD-IPMN with no HRS and WF can undergo surveillance.
- Difficult cases (patients with different indications according to the current guidelines, meaning surgery versus follow-up or endoscopic procedures) should always be referred to a multidisciplinary group in high-volume centers to provide a patient-tailored approach to better tip the scale between the risk of pancreatic cancer and the risk of unnecessary major pancreatic resection.

Pearls and Pitfalls

- Despite IPMNs may evolve towards malignancy, most cysts can be safely surveilled over time.
- Surgery represent the gold standard in case of high risk for malignant degeneration with the goal of cancer prevention or treatment at the earliest stage.
- The risk assessment is still entrusted to a few clinical and radiological features that have high sensitivity but low specificity to detect cancer.

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Future Perspectives

- Prospective observational studies considering both patients undergoing surgery and under surveillance are needed to achieve a better understanding of the natural history of IPMNs.
- Both cyst fluid biosignature and microbiota, will potentially solve two unanswered major concerns: which cysts have a high risk of malignant degeneration? It is safe to discontinue surveillance in case of cyst at extremely low-risk?

49.1 Epidemiology and Biology of IPMNs

Due to the overuse of high-quality cross-sectional imaging, such as CT-scan or Magnetic Resonance Imaging (MRI), the prevalence of incidentally discovered pancreatic cystic neoplasms has dramatically increased [1]. Among pancreatic cysts, intraductal papillary mucinous neoplasms of the pancreas (IPMNs) have a prevalence ranging from 20% to 80% of cases [2, 3].

As IPMNs may progress to cancer following the adenoma-to-carcinoma sequence [4], patients suffering from this condition represent the ideal population where to address efforts in order to prevent pancreatic cancer or diagnose it at the earliest stage.

Whereas in the first years after their discovery, IPMNs were treated aggressively, the progressive availability of new evidences has highlighted how most of cases can be safely surveilled over time due to the low risk of malignant progression.

The risk of malignancy differs among IPMN subtypes. From a morphological point of view, IPMN can be distinguished on the basis of the involvement of main pancreatic duct (MPD). The main duct type (MD-IPMN) originates directly from the MPD (Fig. 49.1). The branch duct type (BD-IPMN) originates from secondary

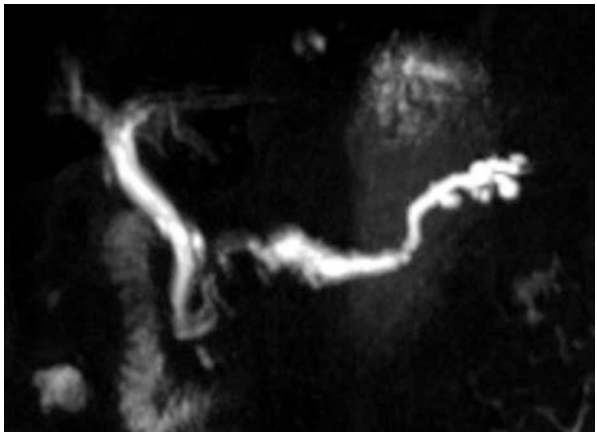

Fig. 49.1 Main duct IPMN

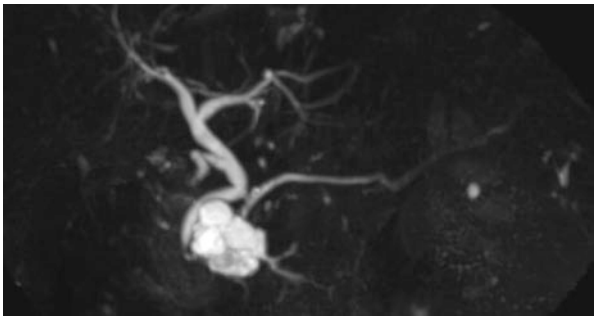

Fig. 49.2 Branch-duct IPMN

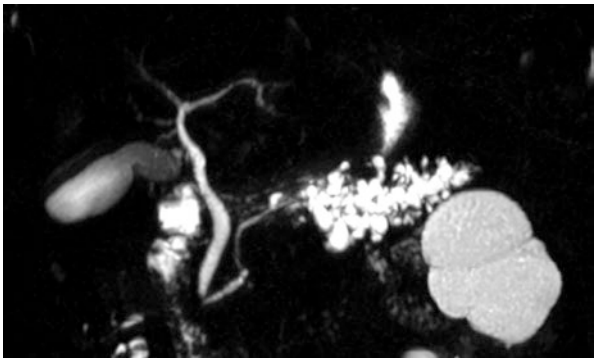

Fig. 49.3 Mixed type IPMN

ducts and does not involve MPD. (Fig. 49.2) The mixed type IPMN (MT-IPMN) represents a combination of both MD- and BD-IPMN since a branch duct dilatation is associated with an involvement of MPD (Fig. 49.3). Surgical series report a lower risk of malignancy in case of BD-IPMNs (6–46%) compared to MD- and MT-IPMN (60–92%) [5, 6].

Beyond the morphological classification that relies on radiological features, also the pathological classification of IPMNs has identified several entities with different risk of cancer [7, 8].

Based on the immunohistochemical characteristics of the epithelium, IPMNs can be distinguished in four subtypes: intestinal (expressing MUC2 and CDX2), pancreato-biliary (expressing MUC1 and MUC6), gastric (expressing MUC5AC) and oncocytic (expressing MUC1 and sometimes MUC6) subtypes. Whereas gastric and intestinal subtypes are the most common [9], the pancreato-biliary type is associated with the highest incidence of invasive carcinoma that is reported in about 90% of cases. IPMNs can show more than one epithelial subtypes, but the oncocytic type is the only subtype that usually can be found alone [9, 10]. The oncocytic subtype shows different characteristics compared to the others (i.e. it lacks both KRAS and GNAS mutations, but shows mutations in ARHGAP26, ASXL1, EPHA8 and ERBB4 genes) [11, 12] and therefore it could represent a separate entity from the other IPMNs. By intersecting morphological and pathological classifications,

the only available evidences show how intestinal subtype are mainly MD-IPMNs [13] and gastric subtypes are predominantly BD-IPMNs [14].

Recently, a two-tier classification system has been proposed by WHO (including only low and high grade dysplasia) in order to improve pathological reporting and align it with the clinical practice [15].

Also, invasive-IPMNs represent an heterogenous group of disease entities that shows different histological differentiations: colloid, tubular and oncocytic [16]. Colloid carcinoma usually arises from intestinal-type epithelial differentiation and is associated with an indolent behavior. Tubular adenocarcinoma is often associated with the gastric and pancreato-biliary subtypes and prognosis is similar to that of pancreatic ductal adenocarcinoma (PDAC) [16]. Oncocytic carcinoma derives from the uncommon oncocytic differentiation of the epithelial component and has a better prognosis if compared to PDAC.

49.1.1 Clinical Presentation and Symptoms

Even if most of cases of IPMN are incidentally discovered during cross-sectional imaging performed for other reasons, patients affected by IPMNs usually complaints of several symptoms [17]. Episodic abdominal pain, heartburn, bloating and post-prandial fullness are reported by 14–32% of patients. However, these symptoms do not correlate specifically with the presence of an IPMN, nor help in scaling the risk of malignancy. Few signs and symptoms can be directly related to the presence of the cyst: obstructive jaundice in case of a solid component of an IPMN located in the pancreatic head; acute abdominal pain in the upper quadrants radiating to the back due to acute pancreatitis produced by mucin plugs that obstruct MPD; new-onset or worsening diabetes mellitus and steatorrhea due to exocrine insufficiency produced by chronic obstructive pancreatitis due to a solid component arising from an IPMN; weight loss and chronic abdominal pain radiating to the back due to a malignant IPMN invading celiac plexus [18, 19]. These specific symptoms have been associated with high-grade dysplasia or invasive carcinoma [20, 21] and both International Association of Pancreatology (IAP) and European guidelines correlate these symptoms with an high risk of malignancy [22, 23].

49.2 Diagnosis of IPMNs

Current diagnostic work-up in case of presumed IPMN usually requires different imaging techniques. At this stage, it is crucial to correctly identify a presumed IPMN by distinguishing it from other pancreatic cystic neoplasms and to scale the risk of malignancy. Usually, CT scan, MRI and contrast-enhanced endoscopic ultrasound (CE-EUS) are the imaging techniques of choice. MRI with magnetic resonance cholangiopancreatography (MRCP) has shown to be superior to the other

techniques in identifying the connection between the cyst and the MPD which is a fundamental prerequisite for the diagnosis of a presumed IPMN. Moreover, contrast-enhanced MRI is particularly accurate in characterizing mural nodules and septations [1, 7].

49.2.1 Diagnostic Accuracy from Imaging

The diagnostic accuracy varies between different techniques: CT-scan has 71–80% accuracy in differentiating between benign and malignant cysts, and 80% accuracy in detecting MPD communication [24]; MRI/MRCP has 55–76% accuracy in differentiating benign and malignant cyst and 96% accuracy in detecting MPD communication [24]; CE-EUS has 65–96% accuracy in differentiating between benign and malignant cysts [25, 26]. MRCP and CT scan are the first line options for IPMN characterization [1, 27], while CE-EUS should be considered only in those patients with unclear radiographic characterization of the pancreatic lesion due to the invasiveness of the procedure that is reported to have an overall complication rate of approximately 2.2% [28]. EUS is an operator-dependent examination but is able to detect mural nodules and differentiate between mucin plugs and/or mural nodules when associated with contrast enhancement (CE) and color-doppler [29, 30]. In recent times new endoscopic techniques have been proposed in order to have a better and more precise assessment of the pancreatic cysts: micro-forceps biopsy [31], confocal laser endomicroscopy [32] or the peroral pancreatoscopy [33].

CE-EUS represents the ideal technique to obtain fine needle aspiration cytology of solid components and cyst fluid analysis including both cytology and assessment of biomarkers. Analysis of CEA level using a cutoff of 192–200 ng/ml and cystic fluid amylase level seems to be useful to differentiate mucinous from non-mucinous pancreatic cystic neoplasms [34, 35]. Recent studies reports that CE-EUS with FNA has 72% sensitivity and 80% accuracy in detecting invasive carcinoma or high grade dysplasia [36]. In the next future, DNA testing of the pancreatic cyst fluid will help in distinguishing between mucinous pancreatic cystic neoplasms, premalignant pancreatic cystic neoplasms and advanced neoplasia [37, 38]. KRAS and GNAS mutations have been detected in more than 90% of IPMNs [38, 39]. Micro-RNAs and glycoproteins altered expression might be the key to identify cysts at high risk of malignant degeneration regardless their morphological features [36, 40–44].

49.3 Management of IPMNs: Surgery vs. Follow-Up

Surgery for IPMNs plays a crucial role since can represent an act of cancer prevention or an act of cure when pancreatic cancer is at the earliest stage. For these reasons, the target of surgery is represented by IPMNs at high risk of malignant progression.

The management of IPMNs has always been based on clinical and radiological features able to predict the risk of cancer [1, 27, 45–47]. The available guidelines [1, 27, 46, 48] (Table 49.1) distinguish between relative and absolute indication for surgery. Obstructive jaundice in case of an IPMN of the head of the pancreas, enhancing mural nodules ≥5 mm, a solid mass, a positive cytology or an MPD ≥10 mm are absolute indications for surgical resection if the patient is fit for surgery, both according to IAP [27] and European evidence-based guidelines [1]. IAP

Table 49.1 Absolute and relative indications for IPMN surgical resection by 2018 European, 2017 IAP, 2015 AGA and 2018 ACG guidelines

	Absolute indications for surgery	Relative indications for surgery
2018 European guideline	Positive cytology for malignancy/HGD Solid mass Jaundice (IPMN related) Enhancing mural nodule (≥5 mm) MPD dilatation ≥10 mm	Growth-rate ≥5 mm/year Increased levels of serum CA 19.9 (>37 U/m) MPD dilatation between 5 and 9.9 mm Cyst diameter ≥40 mm New onset of diabetes mellitus Acute pancreatitis (caused by IPMN) Enhancing mural nodule (<5 mm)
2017 IAP guideline	Cytology suspicious or positive for malignancy Jaundice (IPMN related) Enhancing mural nodule (≥5 mm) MPD dilatation ≥10 mm	Growth-rate ≥5 mm/2 years Increased levels of serum CA 19.9 MPD dilatation between 5 and 9 mm Cyst diameter ≥30 mm Acute pancreatitis (caused by IPMN) Enhancing mural nodule (<5 mm) Abrupt change in caliber of MPD with distal pancreatic atrophy Lymphadenopathy Thickened/enhancing cyst walls
2015 AGA guideline	MPD ≥ 5 mm (on MRI AND EUS) AND solid component OR cytology positive for malignancy	
2018 ACG guideline	Decided by multidisciplinary team. Referral in case of: Jaundice (IPMN related) Acute pancreatitis (caused by IPMN) Increased levels of serum CA 19.9 Mural nodule/solid component MPD dilatation >5 mm Cyst diameter ≥30 mm Positive cytology for malignancy/HGD	

ACG American College of Gastroenterology, *AGA* American Gastroenterological Association, *CA 19.9* cancer antigen 19.9, *EUS* endoscopic ultrasound, *HGD* high-grade dysplasia, *IAP* International Association of Pancreatology, *IPMN* intraductal papillary mucinous neoplasm, *MRI* magnetic resonance imaging, *PD* pancreatic duct

guidelines [27] identifies other specific clinical and radiological characteristics: the *worrisome features*. In presence of at least one between growth rate ≥5 mm over 2 years, increased levels of serum CA19–9, MPD dilatation between 5 and 9.9 mm, cyst diameter ≥30 mm, acute pancreatitis caused by IPMN, enhancing mural nodule <5 mm, abrupt change in the caliber of MPD with distal pancreatic atrophy, lymphadenopathy and thickened/enhancing cyst walls, patients must be evaluated with EUS in order to better scale the risk of malignancy. After EUS, patients become surgical candidates only in presence of MPD features suspicious for involvement, positive cytology or definite mural nodule ≥5 mm. Otherwise, patients can be safely sent to surveillance according to cyst size.

On the other hand, European evidence-based guidelines [1] propose seven additional relative indications for surgery: growth rate ≥5 mm per year, increased levels of serum CA19-9 (>37 U/mL), MPD dilatation between 5 and 9.9 mm, cyst diameter ≥40 mm, new- onset diabetes mellitus, acute pancreatitis caused by IPMN, enhancing mural nodule <5 mm. Surgery is suggested in fit patients presenting at least one relative indication for surgery, while at least two features are required if the patient present with relevant comorbidities. According to European guidelines, surveillance is scheduled on the basis of presence or absence of relative indications for surgery.

American Gastroenterological Association (AGA) Guidelines for the management of asymptomatic neoplastic pancreatic cysts [46] suggest surgery in presence of an MPD ≥5 mm (on MRI and EUS) concomitant to a solid component or cytology positive for malignancy. EUS is suggested in presence of at least two high-risk features such as size ≥30 mm, a dilated MPD or in presence of a solid component.

In absence of indication for surgical resection, clinical and radiological surveillance is recommended. According to IAP guidelines [27], surveillance can be scheduled on the basis of cyst size: for cyst <10 mm CT/MRI in 6 months from diagnosis, then every 2 years if no change; for cysts of 10–20 mm CT/MRI every 6 months in the first year, then yearly for 2 years, then every 2 years if no change; for cysts of 20–30 mm EUS in 3–6 months, then every year alternating MRI with EUS; >30 mm alternating MRI and EUS every 3–6 months. In the last two cases, surgery is recommended in young and fit patients with a long-life expectancy.

European guidelines [1], instead, set surveillance intervals on the basis of the risk of cancer. In absence of absolute or relative indications for surgery, clinical evaluation, serum Ca19.9 and MRI and/or EUS are recommended every 6 months for the first year and then yearly. In presence of a single relative indication for surgery in a patient with significant comorbidities, surveillance should be intense with clinical evaluation, serum Ca19.9 e MRI and/or EUS every 6 months.

Both IAP and European guidelines suggest a lifelong surveillance since evidences supporting a safe follow-up discontinuation should be considered only as preliminary data [49].

Despite this assumption, AGA guidelines [46] suggest surveillance with a new MRI in one year, then every 2 years for a total of 5 years if the cyst remain stable. At this last timepoint, surveillance can be discontinued.

49.3.1 Referral for Work-Up and Decision-Making

Given the complexity of diagnostic workup of IPMNs, patients presenting clinical and radiological characteristics of high risk of malignancy should be referred to high-volume centers and discussed in a multidisciplinary group before undergoing a surgical resection.

Since the goal of surgery for IPMN is prevention of cancer or treatment in its earliest stage, oncological major pancreatic resections are the gold standard. Pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy are the surgical treatment recommended on the basis of the disease extension. Recently, the advancements in minimally invasive surgery techniques and technologies have shown that it is feasible also for IPMN patients [50–52].

49.3.1.1 Resection for IPMN

Even if several centers have experience in this regard [53], parenchyma sparing non-oncological procedures such as middle pancreatectomy or enucleation should be avoided or limited to very selected cases. The surgical strategy for multifocal BD-IPMN should be based on the risk of malignancy of each single cyst and only high risk cysts should be resected [1]. Modern literature disagree regarding the presence of higher or equal risk of degeneration between multifocal and unifocal BD-IPMN, leaving a more aggressive approach only in those patients with a familiar history of PDAC [54–56]. In patients with MD-IPMN, surgical resection is the treatment of choice but there is still no consensus regarding the best surgical options between partial pancreatectomy and close postoperative follow-up of total pancreatectomy with follow-up scheduled only on the basis of final pathological findings [52, 57].

Intraoperative frozen sections of the surgical margin in case of partial are recommended by all the guidelines to assess the completeness of the resection and the presence of dysplasia in the epithelium of MPD and secondary ducts. According to guidelines, if low grade dysplasia is found in the frozen section further resection is not required [1]. In case of invasive-component, high-grade dysplasia or denuded epithelium, it is recommended to extent the resection until low grade dysplasia or normal epithelium [1].

49.3.1.2 Recurrence Risk and Management

Recurrence of non-invasive IPMN, of invasive IPMN and metachronous PDAC not arising from an IPMN are all possible after surgical resection [58–60]. The importance of a regular postoperative surveillance program is due to the evidence of the increased risk of recurrence: 4%, 25% and 62% respectively after 1-, 5- and 10-year follow-up [58]. Resected patients showed a risk of a new invasive IPMN of 0%, 8%

and 38% after 1-,5- and 10-year follow-up [59]. After 5- and 10-year follow-up, the cumulative incidence of a concomitant PDAC is 4.5% and 5.9% in patients who underwent a prior surgical resection [60]. Therefore, patients should be followed-up and lifelong surveillance is recommended according to IAP and European guidelines. IAP guidelines advice postoperative follow-up every 6 months in patients with a familiar history of PDAC or high grade dysplasia at resection margin or in the presence of non-intestinal subtype of IPMN [27]. Instead, European guidelines recommend a follow-up every 6 month for the first 2 years and after an yearly surveillance if the IPMN had high grade dysplasia or MPD involvement [1]. In absence of invasive component, surveillance is not required if a total pancreatectomy is performed. In presence of an invasive-IPMN, regardless the type of major pancreatectomy, follow-up schedule must be similar to that of PDAC.

49.4 Conclusion

Despite recent advances, the complete understanding of the natural history of IPMN has not yet been reached. New evidences from large observational studies will provide insights on cyst's biosignature. However, the heterogeneity of features characterizing these pancreatic cysts currently requires a multidisciplinary discussion in the context of high-volume centers in all cases, to better tip the balance between risk of cancer and that of an unnecessary major pancreatic resection.

References

1. Del Chiaro M, et al. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018; https://doi.org/10.1136/gutjnl-2018-316027.
2. Castillo CF, Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas. Gastroenterology. 2010;139:708–713.e2.
3. Sahora K, Castillo C F-d. intraductal papillary mucinous neoplasms. Clin Opin Gastroenterol. 2015;31:424–9.
4. Sugiyama M, Suzuki Y. Natural history of IPMN: adenoma-carcinoma sequence in IPMN. In: Beger HG, et al., editors. Pancreatic cancer, cystic neoplasms and endocrine tumors: diagnosis and management. Hoboken, NJ: Wiley; 2015. https://doi.org/10.1002/9781118307816.ch30.
5. Sahora K, et al. Not all mixed-type intraductal papillary mucinous neoplasms behave like main-duct lesions: Implications of minimal involvement of the main pancreatic duct. Surgery. 2014; https://doi.org/10.1016/j.surg.2014.04.023.
6. Sahora K, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale?. A critical analysis of the revised international consensus guidelines in a large single-institutional series. Ann Surg. 2013; https://doi.org/10.1097/SLA.0b013e3182a18f48.
7. Bosman F, Carneiro F, Hruban R, Theise N. WHO classification of tumours of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010. https://doi.org/10.1017/CBO9781107415324.004.
8. Adsay V, et al. Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract:

recommendations of verona consensus meeting. Ann Surg. 2016; https://doi.org/10.1097/SLA.0000000000001173.
9. Furukawa T, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut. 2011;60:509–16.
10. Distler M, et al. Pathohistological subtype predicts survival in patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Ann Surg. 2013; https://doi.org/10.1097/SLA.0b013e318287ab73.
11. Basturk O, et al. Distinct pathways of pathogenesis of intraductal oncocytic papillary neoplasms and intraductal papillary mucinous neoplasms of the pancreas. Virchows Arch. 2016; https://doi.org/10.1007/s00428-016-2014-x.
12. Basturk O, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. Mod Pathol. 2016; https://doi.org/10.1038/modpathol.2016.98.
13. Adsay NV, et al. Colloid (mucinous noncystic) carcinoma of the pancreas. Am J Surg Pathol. 2001; https://doi.org/10.1097/00000478-200101000-00003.
14. Terris B, et al. Mucin gene expression in intraductal papillary-mucinous pancreatic tumours and related lesions. J Pathol. 2002; https://doi.org/10.1002/path.1146.
15. Basturk O, et al. A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol. 2015; https://doi.org/10.1097/PAS.0000000000000533.
16. Mino-Kenudson M, et al. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. Gut. 2011; https://doi.org/10.1136/gut.2010.232272.
17. Perri G, et al. Management of pancreatic cystic lesions. Dig Surg. 2019; https://doi.org/10.1159/000496509.
18. Sakorafas GH, Sarr MG. Cystic neoplasms of the pancreas: what a clinician should know. Cancer Treat Rev. 2005; https://doi.org/10.1016/j.ctrv.2005.09.001.
19. Stark A, Donahue TR, Reber HA, Joe Hines O. Pancreatic cyst disease a review. JAMA. 2016; https://doi.org/10.1001/jama.2016.4690.
20. Tsutsumi K, et al. A history of acute pancreatitis in intraductal papillary mucinous neoplasms of the pancreas is a potential predictive factor for malignant papillary subtype. Pancreatology. 2010; https://doi.org/10.1159/000320696.
21. Ingkakul T, et al. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. Ann Surg. 2010; https://doi.org/10.1097/SLA.0b013e3181c5ddc3.
22. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007; https://doi.org/10.1111/j.1572-0241.2007.01516.x.
23. Suda K, et al. Variant of intraductal carcinoma (with scant mucin production) is of main pancreatic duct origin: a clinicopathological study of four patients. Am J Gastroenterol. 1996;
24. Jones MJ, et al. Imaging of indeterminate pancreatic cystic lesions: a systematic review. Pancreatology. 2013; https://doi.org/10.1016/j.pan.2013.05.007.
25. Sultana A, et al. What is the best way to identify malignant transformation within pancreatic IPMN: a systematic review and meta-analyses. Clin Transl Gastroenterol. 2015; https://doi.org/10.1038/ctg.2015.60.
26. Tirkes T, et al. Cystic neoplasms of the pancreas; findings on magnetic resonance imaging with pathological, surgical, and clinical correlation. Abdom Imaging. 2014; https://doi.org/10.1007/s00261-014-0138-5.
27. Tanaka M, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738–53.
28. Lee LS, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. Clin Gastroenterol Hepatol. 2005; https://doi.org/10.1016/S1542-3565(04)00618-4.

29. Yamashita Y, et al. Usefulness of contrast-enhanced endoscopic sonography for discriminating mural nodules from mucous clots in intraductal papillary mucinous neoplasms a single-center prospective study. J Ultrasound Med. 2013; https://doi.org/10.7863/jum.2013.32.1.61.
30. Matsumoto K, et al. Performance of novel tissue harmonic echo imaging using endoscopic ultrasound for pancreatic diseases. Endosc Int open. 2016; https://doi.org/10.1055/s-0034-1393367.
31. Zhang ML, et al. Moray micro forceps biopsy improves the diagnosis of specific pancreatic cysts. Cancer Cytopathol. 2018; https://doi.org/10.1002/cncy.21988.
32. Tsujino T, et al. In vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy. Best Pract Res Clin Gastroenterol. 2015; https://doi.org/10.1016/j.bpg.2015.06.006.
33. Yamaguchi T, Kita E, Mikata RHT. Peroral pancreatoscopy (POPS). New York, NY: Springer; 2019. https://doi.org/10.1007/978-4-431-56009-8_31.
34. Tanaka M, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012; https://doi.org/10.1016/j.pan.2012.04.004.
35. Brugge WR, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004; https://doi.org/10.1053/j.gastro.2004.02.013.
36. Matthaei H, et al. miRNA biomarkers in cyst fluid augment the diagnosis and management of pancreatic cysts. Clin Cancer Res. 2012; https://doi.org/10.1158/1078-0432.CCR-12-0035.
37. Wu J, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc Natl Acad Sci. 2011; https://doi.org/10.1073/pnas.1118046108.
38. Amato E, et al. Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol. 2014; https://doi.org/10.1002/path.4344.
39. Wu J, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011; https://doi.org/10.1126/scitranslmed.3002543.
40. Ryu JK, et al. Elevated microRNA miR-21 levels in pancreatic cyst fluid are predictive of mucinous precursor lesions of ductal adenocarcinoma. Pancreatology. 2011; https://doi.org/10.1159/000329183.
41. Caponi S, et al. The good, the bad and the ugly: a tale of miR-101, miR-21 and miR-155 in pancreatic intraductal papillary mucinous neoplasms. Ann Oncol. 2013; https://doi.org/10.1093/annonc/mds513.
42. Grüner BM, et al. MALDI imaging mass spectrometry for in situ proteomic analysis of preneoplastic lesions in pancreatic cancer. PLoS One. 2012; https://doi.org/10.1371/journal.pone.0039424.
43. Mann BF, Goetz JA, House MG, Schmidt CM, Novotny MV. Glycomic and proteomic profiling of pancreatic cyst fluids identifies hyperfucosylated lactosamines on the *N*-linked glycans of overexpressed glycoproteins. Mol Cell Proteomics. 2012; https://doi.org/10.1074/mcp.M111.015792.
44. Corcos O, et al. Proteomic assessment of markers for malignancy in the mucus of intraductal papillary mucinous neoplasms of the pancreas. Pancreas. 2012; https://doi.org/10.1097/MPA.0b013e3182289356.
45. Del Chiaro M, et al. European experts consensus statement on cystic tumours of the pancreas. Dig Liver Dis. 2013;45:703–11.
46. Vege SS, Ziring B, Jain R, Moayyedi P. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:819–22.
47. Rubio-Tapia A, et al. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013; https://doi.org/10.1038/ajg.2013.79.
48. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018; https://doi.org/10.1038/ajg.2018.14.

49. Marchegiani G, et al. 'Trivial' cysts redefine the risk of cancer in presumed branch-duct intraductal papillary mucinous neoplasms of the pancreas: a potential target for follow-up discontinuation? Am J Gastroenterol. 2019; https://doi.org/10.14309/ajg.0000000000000378.
50. Scholten L, et al. Surgical management of intraductal papillary mucinous neoplasm with main duct involvement: an international expert survey and case-vignette study. Surgery. 2018; https://doi.org/10.1016/j.surg.2018.01.025.
51. Watanabe Y, et al. Validity of the management strategy for intraductal papillary mucinous neoplasm advocated by the international consensus guidelines 2012: a retrospective review. Surg Today. 2016; https://doi.org/10.1007/s00595-015-1292-2.
52. Tamura K, et al. Treatment strategy for main duct intraductal papillary mucinous neoplasms of the pancreas based on the assessment of recurrence in the remnant pancreas after resection: a retrospective review. Ann Surg. 2014; https://doi.org/10.1097/SLA.0b013e3182a690ff.
53. Bassi C. Middle segment pancreatectomy: a useful tool in the management of pancreatic neoplasms. J Gastrointest Surg. 2007; https://doi.org/10.1007/s11605-007-0129-8.
54. Schmidt CM, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007; https://doi.org/10.1097/SLA.0b013e318155a9e5.
55. Fritz S, et al. Clinicopathologic characteristics of patients with resected multifocal intraductal papillary mucinous neoplasm of the pancreas. Surgery. 2012; https://doi.org/10.1016/j.surg.2012.05.025.
56. Shi C, et al. Increased prevalence of precursor lesions in familial pancreatic cancer patients. Clin Cancer Res. 2009; https://doi.org/10.1158/1078-0432.CCR-09-0004.
57. Ito T, et al. The distribution of atypical epithelium in main-duct type intraductal papillary mucinous neoplasms of the pancreas. J Hepatobiliary Pancreat Sci. 2011; https://doi.org/10.1007/s00534-010-0337-6.
58. He J, et al. Is it necessary to follow patients after resection of a benign pancreatic intraductal papillary mucinous neoplasm? J Am Coll Surg. 2013; https://doi.org/10.1016/j.jamcollsurg.2012.12.026.
59. Kang MJ, et al. Long-term prospective cohort study of patients undergoing pancreatectomy for intraductal papillary mucinous neoplasm of the pancreas. Ann Surg. 2014; https://doi.org/10.1097/SLA.0000000000000470.
60. Miyasaka Y, et al. Predictive factors for the metachronous development of high-risk lesions in the remnant pancreas after partial pancreatectomy for intraductal papillary mucinous neoplasm. Ann Surg. 2016; https://doi.org/10.1097/SLA.0000000000001368.

Chapter 50
Pancreatic Cystic Lesions and Risk of Cancer

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Take Home Messages

- Cystic lesions in the pancreas are common
- Most cysts are benign, but some should be resected due to malignant risk
- Cyst characteristics to aid in decision involves imaging studwies, cyst fluid evaluation and clinical features, but none have perfect accuracy for prediction of risk
- Novel and more comprehensive risk tools may aid in optimal decision making in the near future

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Pearls and Pitfalls
- Guidelines are currently based on consensus made from poor level data
- Guidelines are not uniform in their criteria nor recommendations
- Currently, a given decision to resect or observe each comes with risk for over- and under-treatment

Future Perspective
- Better tools to differentiate cyst types and malignancy risk are needed
- Population-based, longitudinal studies are needed to better define true epidemiology, true prevalence and true cancer-risk in pancreatic cysts
- Novel techniques, including cyst fluid investigations, liquid biopsies, machine learning and artificial intelligence may help improve decision-making and reduce over- and under-treatment

50.1 Introduction

Pancreatic cystic lesions are becoming more prevalent due to the increasing awareness and increasing employment of cross-sectional imaging as well as an aging population [1, 2] such that they may be found in approximately 8% of an asymptomatic population [3]. Most cystic lesions are benign, but some are neoplastic and have a risk of progressing to cancer. However, distinguishing the variety of cystic lesions can be difficult [4], and often a multidisciplinary approach is necessary to arrive at the best work-up and surveillance strategy, if not considering resection based on consensus criteria [5–8].

Pancreatic cystic lesions (PCL) refer to all cystic lesions of the pancreas (Fig. 50.1), but these are a heterogeneous group of cysts with different malignant potential, radiological cyst characteristics, epidemiological features and management [5, 9]. An increasing number of patients are being referred to pancreatic centers around the world due to often incidentally discovered cystic neoplasms of the pancreas resulting from the increasing availability of high-quality radiological imaging. Although pancreatic cystic neoplasms have certainly always existed, only recently have guidelines for follow-up, diagnosis, and management been issued. Nevertheless, these guidelines themselves are based on the scarce data available and are subject to evolution [4, 5, 8, 10, 11].

This chapter aims to provide an overview of pancreatic cystic lesions, focusing on malignant potential and management options. A general overview of existing guidelines and management options will be presented. Management of Intraductal Papillary Mucinous Neoplasms (IPMN) will be discussed elsewhere in this book.

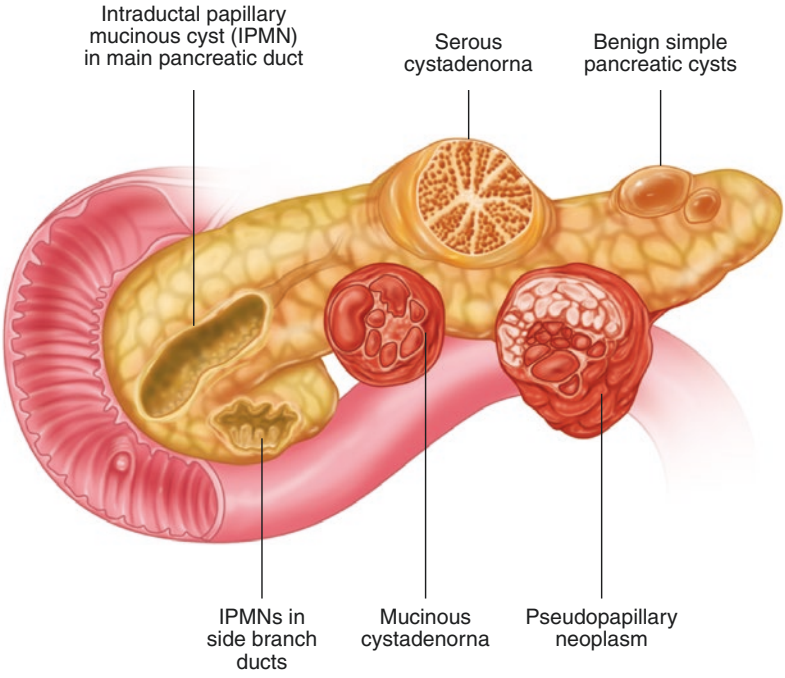


Fig. 50.1 Illustration of different cyst types in the pancreas. *IPMN* intrductal papillary mucinous neoplasia

50.2 Epidemiology of Pancreatic Cystic Lesions

The overall prevalence of PCL in the general population ranges from 2.6% to 15%, but increase with age to 27% in patients >80 years [12]. Pancreatic cysts are classified according to the WHO 2019 histological classification (Table 50.1) [13]. While radiological imaging can distinguish classical features such that benign, premalignant and malignant lesions may be determined, the overall problem is that the definite classification of a cyst can be difficult before it is surgically resected and histologically examined. The accuracy of the preoperative diagnosis varies from 47% to 78% when compared to the final histological diagnosis [14–16]. Thus, the surgeon has to balance the risk of malignancy with the possible morbidity and mortality associated with pancreatic surgery. The decision-making must account for a possible erroneous preoperative diagnosis such that some patients will inevitably be subject to surgery later deemed unnecessary. The diagnostic accuracy is however improving and likely will continue to improve in the future due to the improved

Table 50.1 WHO classification of pancreatic cystic lesions

Epithelial neoplastic	**Epithelial non-neoplastic**
Intraductal papillary mucinous neoplasm (IPMN)	Lymphoepithelial cyst
Mucinous cystic neoplasm (MCN)	Mucinous non-neoplastic cyst
Serous cystic neoplasm (SCN)	Enterogeneous cyst
Serous cystadenocarcinoma	Retention cyst/dysontogenic cyst
Cystic neuroendocrine tumor	Peri-ampullary duodenal wall cyst
Acinar cell cystadenoma	Endometrial cyst
Cystic acinar cell carcinoma	Congenital cyst
Solid pseudopapillary neoplasm (SPN)	
Accessory-splenic epidermoid cyst	
Cystic hamartoma	
Cystic teratoma (dermoid cyst)	
Cystic ductal adenocarcinoma	
Cystic pancreatoblastoma	
Cystic metastatic epithelial neoplasm	
Others	
Non-epithelial neoplastic	**Non-epithelial non-neoplastic**
Benign non-epithelial neoplasm (e.g., Lymphangioma)	Pancreatitis associated pseudocyst
Malignant non-epithelial neoplasms (e.g., sarcomas)	Paracitic cyst

Developed from Bosman FT, Carneiro F, Hruban RH, et al. WHO classification of tumours of the digestive system: World Health Organization, 2010

accuracy of radiological imaging, increasing utilisation of EUS (Fig. 50.2) but also the implementation of molecular and genetic analysis [12]. Pancreatic cysts vary in malignant potential however there is an overall increased risk in pancreas cancer with the presence of a pancreatic cyst which may be increased as high as 20-fold compared to the general population [17].

50.3 Contemporary Guidelines for Pancreatic Cysts

With the increasing focus on pancreas cysts, several guidelines for the diagnostic workup and management have evolved, with *four clinical guidelines* now in place, including the International Association of Pancreatology (Fukuoka) guidelines [18], European Study Group on Cystic Tumours of the Pancreas [19], American Gastroenterological Association (AGA) [20] and American College of Gastroenterology (ACG) clinical guideline [21]. Furthermore, the American College of Radiologists (ACR) have issued a "white paper" on recommendations for surveillance modalities and intervals for incidentally discovered pancreatic cysts [22]. While this paper contains several useful algorithms and flow charts, it has seen less penetrance into clinical practice compared to the other clinical guidelines. While there is consensus that the risk of malignancy should be balanced against the life-expectancy and comorbidities, the indications for surgery and surveillance

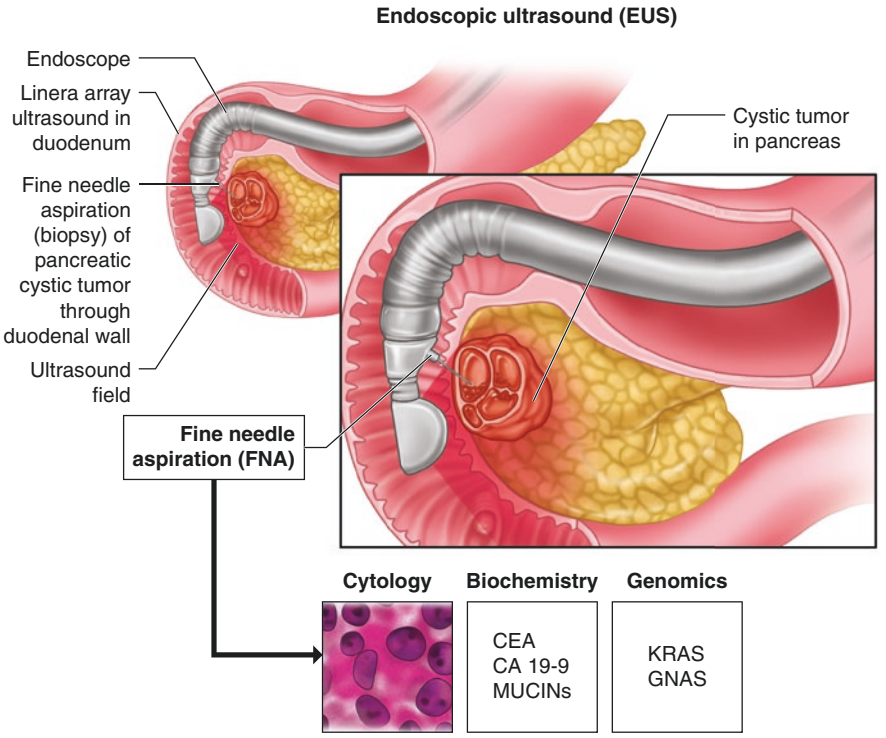


Fig. 50.2 Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) for cyst diagnostics. *EUS* endoscopic ultrasound, *FNA* fine needle aspiration, *CEA* carcinoembryonic antigen

strategies vary among the guidelines [23]. At the time of writing, there is work underway to merge and suggest a common set of guidelines to avoid the confusion generated by having several competing opinions. This chapter will refer to the guidelines where applicable and to ongoing areas of research with relevance to pancreatic cysts.

50.4 Types of Cysts in the Pancreas

Several types of cystic lesions (Fig. 50.1, Table 50.1) in the pancreas may occur and consideration of the clinical context is important to enable the best diagnostic strategy and determine the requirement for further treatment or surveillance. While some lesions, such as a pancreatic pseudocyst, are relatively common particularly following a recent episode of acute pancreatitis, often lesions are deemed 'incidental' (detected on imaging performed for other indications) rather than being detected following investigations indicated by symptoms.

In addition to common cystic lesions, one must consider the possible presentation of rarer entities; including cystic pancreatic neuroendocrine tumors (cystic PanNET), lymphoepithelial cysts [24], pancreatic echinococcus/hydatic cyst [25, 26], pancreatic cystic lymphangioma [27] or hemolymphangioma [28], true congenital pancreatic cyst [29], or tuberculosis [30], to mention but a few rare examples (Table 50.1). This chapter will primarily give an overview of PCLs, focusing on those considered neoplastic and those which harbour malignant potential.

50.4.1 Cyst Characteristics

PCLs can be either neoplastic (PCN) or non-neoplastic (Table 50.1). Non-neoplastic lesions exhibit no malignant potential and rarely require treatment unless symptomatic. Non-neoplastic cysts can be divided into non-epithelial and epithelial cysts. Pancreatic pseudocysts are the most common non-epithelial and also the most common pancreatic cystic lesion overall [31], while retention cysts are the most common epithelial. Non-neoplastic lesions have no malignant potential and require treatment only if symptomatic.

50.4.2 Non-epithelial Inflammatory Fluid Collections

According to the 2012 revised Atlanta classification of acute pancreatitis [32], non-epithelial inflammatory fluid collections were classified into acute peripancreatic fluid collections, pancreatic pseudocysts, acute necrotic collections and walled off necrosis (WON) of the pancreas according to the presence of necrosis and temporal relation to presentation. Acute peripancreatic fluid collections occur within 4 weeks of interstitial pancreatitis and are fluid collections without a well-defined wall. A pseudocyst describes a mature fluid collection with a well-defined wall and present at least 4 weeks after acute pancreatitis episode. Acute necrotic collections (present within 4 weeks) result from necrotic pancreatitis, contain both fluid and solid material with an ill-defined wall. Walled off pancreatic necrosis is a matured (usually >4 weeks) encapsulated collection of necrosis.

Pancreatic pseudocysts can be found in 5–16% of patients that have had acute pancreatitis and 20–40% of patients with chronic pancreatitis, especially if alcohol consumption is the causative factor [33]. Pseudocysts are usually diagnosed with CT as a rounded well circumscribed fluid collection with enhancing wall. Fine needle aspiration generally performed at EUS (Fig. 50.2) will reveal an amylase rich fluid, containing inflammatory cells with a paucity of epithelial cells [33]. Symptomatic inflammatory fluid collections have traditionally been treated by surgical cystogastrostomy which can be performed laparoscopically, however endoscopic cystogastrostomy with or without lumen opposing stents (Hot AXIOS™) is increasingly the preferred option. Percutaneous drainage is rarely performed for drainage of fluid collections, however it is often the first step if percutaneous necrosectomy is required for management of WON [34].

50.4.3 Epithelial Non-neoplastic Lesions

This is a group of rare non-neoplastic cysts that include retention cysts, squamoid cysts, lymphoepithelial cysts, enterogeneous cysts, mucinous non-neoplastic cysts, endometrial cysts and para-ampullary duodenal cysts. They are non-neoplastic in nature and do not require resection unless symptomatic but may be difficult to distinguish from neoplastic cysts, especially mucinous cysts. Diagnostic dilemma may result in an erroneous resection under the belief that they are neoplastic exposing the patient to the potential dangers of pancreatic surgery [35].

50.5 Pancreatic Cystic Neoplasms (PCN)

Pancreatic cystic neoplasms may harbour potential for malignant transformation and therefore are important to identify and manage appropriately (Figs. 50.1 and 50.3). They are classified as mucinous, (including IPMN and Mucinous Cystic Neoplasm [MCN]) and non-mucinous (Serous cystic neoplasm [SCN], Solid pseudopapillary neoplasms [SPN], cystic Neuroendocrine Tumour [cNET]) according to the epithelial lining and secretions they produce [13]. PCNs may harbor malignant potential and are important to identify and manage appropriately (Table 50.2).

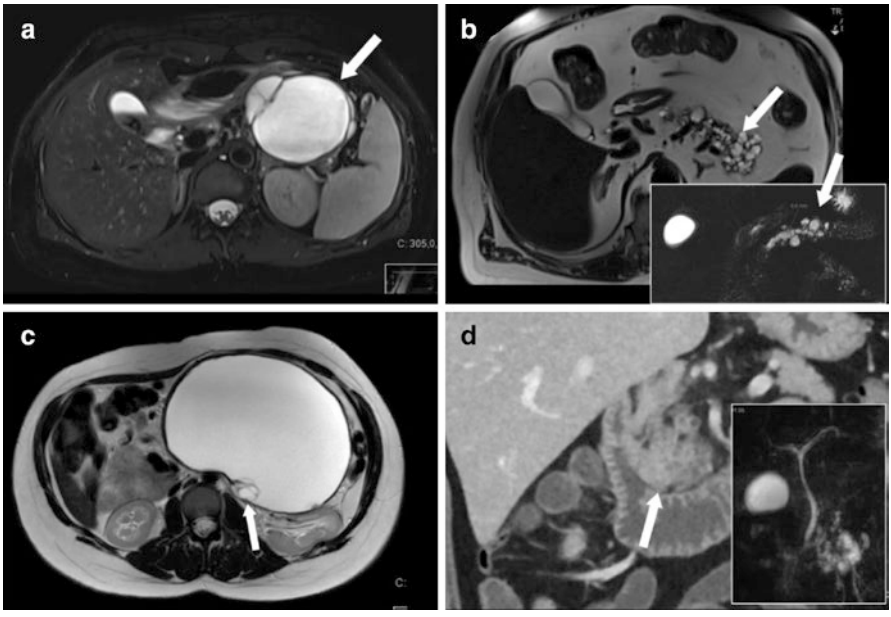


Fig. 50.3 Pancreatic cystic lesions on cross sectional imaging. (**a**) Mucinous cystic neoplasia (MCN) on MRI T2-weighted imaging. (**b**) Mixed type IPMN on MRI (T2 haste), with illustration of side- and main-duct dilatations in insert (arrow). (**c**) Mucinous cystic neoplasi (MCN) on MRI, with invasive component (arrow showing nnodular change within cyst wall). (**d**) Serous cystic lesion on CT (white arrow), with MRI in insert

Table 50.2 PCN key demographic and clinical features

Characteristics	SCN	MCN	IPMN Main duct/mixed	IPMN Sidebranch	SPN	cNET
Age	Variable, usually fifth–seventh decade	Variable, usually fifth–seventh decade	Variable, usually fifth–seventh decade	Variable, usually fifth–seventh decade	Second–third decade	Variable, usually fifth–sixth decade
Gender distribution	70% female	90–95% female	Equal	Equal	90% female	Equal
Clinical presentation	Incidental finding, abdominal pain, mass effect	Incidental finding, abdominal pain or malignancy related	Incidental finding, jaundice, pancreatitis, exocrine insufficiency, malignancy-related	Incidental finding, jaundice, pancreatitis, malignancy-related	Incidental finding, abdominal pain, mass effect	Incidental finding (usually nonfunctioning), abdominal pain, mass effect
Imaging characteristics	Microcystic (honeycomb appearance)	Unilocular, macrocystic	Dilated pancreatic duct	Dilated side branches	Solid and cystic mass	Solid and cystic mass, hypervascular
Connection with main pancreatic duct	No	No	Yes	Yes	No	No
Solitary or multifocal	Solitary	Solitary	Solitary/Multifocal	Solitary/Multifocal	Solitary	Solitary
Malignant potential	Negligible	10–39%	36–100%	11–30%	10–15%	10%

50.5.1 Intraductal Papillary Mucinous Neoplasm (IPMN)

IPMN is a mucin producing papillary neoplasm of the pancreatic duct system representing the most commonly diagnosed and resected PCN. Arising from the main pancreatic duct or side branches it is therefore divided into main duct-IPMN, side branch IPMN and mixed type-IPMN. They can be solitary or multifocal, have equal sex distribution and peak incidence is fifth–seventh decade. All types harbour a malignant potential, however particularly main duct involvement, large size, high growth rate and solid component/mural nodules are associated with higher risk [36–38].

50.5.2 Mucinous Cystic Neoplasm (MCN)

Mucinous cystic neoplasms (Fig. 50.3a, b) occur almost exclusively in women (>95%), are predominately located in the pancreatic body and tail (97%) and arise in the fifth–seventh decade [39], usually younger than IPMN. They are commonly large, septated, thick-walled and lack communication with the ductal system. They contain an epithelial lining of tall mucin secreting cells with typical rich ovarian type stroma [39] and are distinguished from IPMN by the presence of this stroma, as well as non-communication with the ductal system and their typical location in the distal pancreas. MCN are generally solitary while IPMN can be multifocal (Fig. 50.3b). Both type of lesions have similar mucin rich cyst fluid with high CEA levels, however amylase level varies [40]. Mucinous cystic neoplasms carry a significant malignant potential and resection should be considered, especially at a size of >4 cm with any worrisome features [41], as depicted in Fig. 50.3c.The malignant potential of MCN by far exceeds that of IPMN and patients should be offered resection if medically fit for operative intervention. Oncological resection (distal pancreatectomy with splenectomy in 90–95% of cases) with respective lymphadenectomy is advised if susceptive features are present. In MCN without any suspective features a non-oncological resection can be done [19]. Five-year survival after resection of invasive MCN carcinoma is 57%, while non-invasive disease has 100% 5-year disease specific survival [39]. A large multicentre study found a low risk in small MCNs [42], and these may initially be observed.

50.5.3 Serous Cystic Neoplasm (SCN)

Most serous cystic neoplasms are serous cystadenomas (SCA; Fig. 50.3d) that can occur throughout the pancreas. These are benign neoplasms originating from centroacinar cells and are lined by serous glycogen rich cuboidal cells. In almost all cases these tumors are benign, indolent, slow growing and rarely cause any symptoms

[43]. They are most common in women in their sixth decade. Very rarely, malignant serous cystadenocarcinomas can occur as well [44, 45].

A multinational large cohort study from expert centers concludes that surgery should only be offered if diagnosis is uncertain, if the neoplasm causes significant symptoms or in exceptional cases if malignancy is suspected [43]. The tumour typically has a microcystic appearance like a honeycomb or sponge, often with a central scar, but can also be macrocystic or mixed [46]. Von Hippel-Lindau (VHL) patients are prone to develop cysts and neuroendocrine tumours in the pancreas in addition to several other benign and malignant neoplasms. Remarkably, pancreatic cysts occur in approximately 70% of VHL patients, making it the only hereditary tumour syndrome with such a discernible expression of pancreatic cysts.

Loss of function in the tumour suppressor VHL gene is associated with both VHL syndrome cases and sporadic cases of SCA [46]. VHL Cyst fluid is low in CEA and amylase [40].

50.5.4 Solid Pseudopapillary Neoplasm (SPN)

SPN is a rare cystic neoplasm representing 1–3% of exocrine pancreatic neoplasms [47] and are most common in young women (20–30 years) with a female:male ratio of approximately 9:1 [48]. Almost 90% of SPNs reported in the literature are from the period after year 2000 [48], with a large body of reports being case reports or case series, with only occasional, single institutional series of >10 patients prior to that period [49]. More recently, several larger series have been published [50–55].

SPN are classically large (mean size at diagnosis reported at 8.6 cm) [48], well-circumscribed solitary lesions that can have a cystic, solid or mixed appearance [48]. Approximately two thirds are diagnosed based on work-up following presentation with abdominal pain secondary to the mass effect of the tumor, while another third are usually detected incidentally on imaging. SPN can appear anywhere in the pancreas, they are usually benign with low-grade histological changes but 10–20% have a malignant potential [56]. The cyst fluid is haemorrhagic, highly cellular and low in CEA [56]. The aetiology of SPN involves mutations in the gene encoding β-catenin (*CTNNB1*) [57].

The treatment of choice is surgical resection due to their malignant potential [48], but disease course is usually indolent (even for metastatic disease) and usually associated with an excellent prognosis on long-term follow-up (>90% 10-year survival). Surgical resection is recommended for recurrences or even in the presence of liver metastases, as there remains no effective oncological treatment to offer and very good long-term survival can be achieved even in the metastatic setting [50, 51, 54, 58]. If possible, function-preserving surgery is advocated with no need for extended lymph node dissection. A high Ki67 index ≥4% (Fig. 50.4) as a marker of high proliferative activity in the cells may predict the malignant potential and poor prognosis of SPN [53, 59].

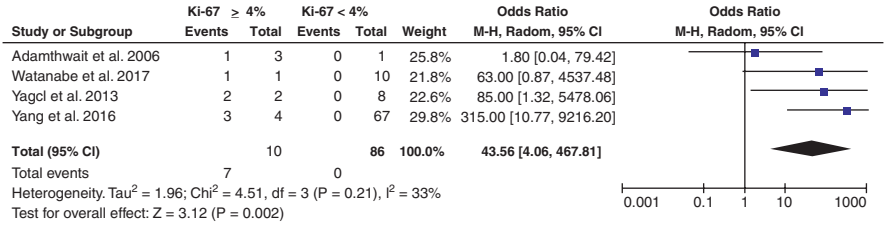


Fig. 50.4 Proliferation activity (Ki-67) and malignancy risk in SPN (Reproduced from Zou C, et al. Meta-analysis of Ki-67 expression for recurrence in patients with solid pseudopapillary tumor of the pancreas. *HPB (Oxford)* 2019 doi: https://doi.org/10.1016/j.hpb.2019.09.018 (in press) with permission from Elsevier)

50.5.5 Cystic Neuroendocrine Tumors (cNET)

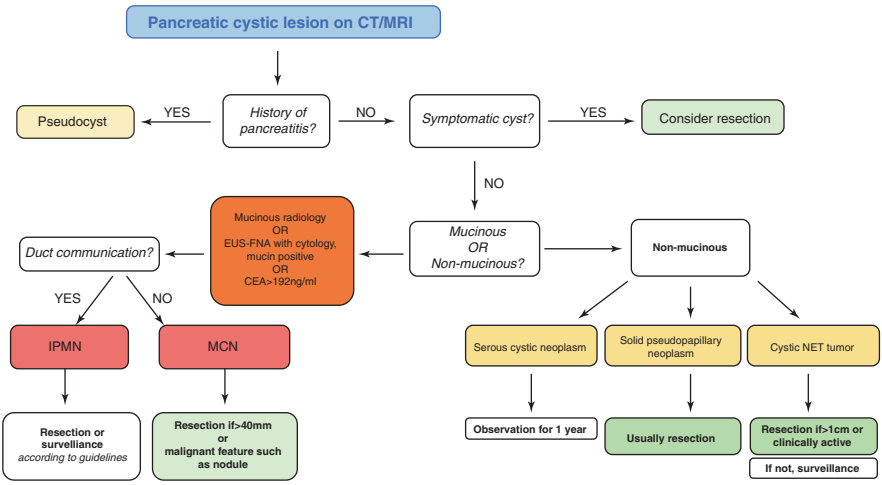
Pancreatic neuroendocrine tumors are typically solid tumors but can sometimes also present as cystic lesions [60]. They have an equal sex distribution and a wide age range with mean age in the sixth decade of life [60]. They can be located anywhere in the pancreas and are difficult to distinguish from other cystic lesions such as IPMN or MCN, making misdiagnosis common [60]. Most of these tumors are non-functional and do not secrete hormones [60]. They have a straw like cyst fluid low on amylase and CEA and do not communicate with the pancreatic duct. Their malignant potential is low and lesions <1 cm are simply managed by surveillance, while patients with larger or clinically active lesions can be offered resection [56].

50.6 Diagnostic Workup of Pancreatic Cystic Lesions

Much remains debated as to the best and optimal management of pancreatic cysts (Fig. 50.5), with several suggestions and views, either holding a conservative attitude or a more aggressive or surgery prone approach to management. It is safe to say that the 'jury is still out' on the most appropriate modality for differentials, diagnostic test to use, markers of risk prediction and the optimal surgical management strategy [4–6, 10, 11, 61]. However, data is accumulating and evidence evolving.

50.6.1 Radiologic Imaging

Diagnosis of a pancreas cyst usually starts with cross sectional imaging, either following cyst symptoms, or due to other unrelated disease giving rise to the commonly found asymptomatic incidentally found pancreatic cyst. MRI has a higher



Legent:
IPMN denotes intraductal papillary mucinous neoplasia; MCN denotes mucinous cystic neoplasia

Fig. 50.5 A suggested flowchart of management of pancreatic cystic lesions. *IPMN* intraductal papillary mucinous neoplasia, MCN mucinous cystic neoplasia

contrast resolution and better sensitivity than CT in detecting PCN but not necessarily a better specificity. The accuracy for identifying the specific type of PCN is 40–95% for MRI and 40–81% for CT [19]. MRI is more sensitive to detect communication with the pancreatic duct, septations, the presence of mural nodules and multifocality and is therefore the imaging modality of choice. A lack of ionizing radiation is of notable importance as many patients are included in surveillance programs [18, 19]. CT should be used for detection of parenchymal, mural and central calcifications, especially when differentiating pseudocysts associated with chronic pancreatitis. CT is useful for excluding and staging malignant disease as well as for follow up of postoperative recurrence in case of malignancy [19].

EUS in addition to contrast enhanced EUS is recommended as an adjunct to cross-sectional imaging. However, EUS is also imperfect in determining the specific type of PCN, yet can assist in distinguishing features associated with malignancy including mural nodules, septations and microvasculature density and blood flow [62, 63]. As such, EUS is recommended if clinical or radiological features of concern are detected during primary work-up or surveillance [19]. Tissue or cystic fluid acquisition is another important value of EUS.

50.6.2 Cyst Fluid Analysis and Cytology

Utilisation of EUS- fine needle aspiration (FNA) varies widely worldwide, with variable indication in the guidelines. EUS-FNA can be used to proof a cyst is mucinous type via a combination of CEA, lipase/amylase concentration and cytological analysis [19]. Cytology can also help to differentiate malignant from benign, if cells are obtained. Determination of KRAS mutational status can help to distinguish mucinous cysts, while the presence of GNAS mutations can help distinguish IPMN from other pancreatic cysts [64, 65].

EUS-FNA has future potential as further molecular and genomic biomarkers in cyst fluid are identified, furthermore novel techniques including cytology brush, mini-biopsy forcipes, cystoscopy and confocal laser endomicroscopy might overcome the common paucity of cellular components in aspirated cyst fluid [66]. In a recent retrospective study the use of EUS-FNA with cytology and biochemical analyses changed the pre EUS-FNA diagnosis in nearly half the patients, especially in young patients with large cysts [67]. Some 55 out of 101 presumed BD-IPMN turned out to be other cyst types such as SCN, simple retention cysts, cNET, pancreatic ductal adenocarcinoma or pseudocysts. Seventeen of 26 presumed MCN turned out to be other cysts, such as SCN, simple retention cysts, SPN, pancreatic ductal adenocarcinoma and neuroendocrine tumours. The initial recommendation changed from surgery to conservative treatment in 61of 90 patients and from initial conservative to surgical treatment in 6 of 98.

50.7 Novel Diagnostic and Risk Tools for Pancreatic Cystic Lesions

There are many new and promising developments in PCL diagnosis (many of which are discussed in more detail in other chapters). Among the radiological developments, a Secretin-enhanced MRCP is used with promising results in some centers. In this technique, the hormone Secretin is given to stimulate the acinar cell secretion which leads to enlargement of the pancreatic ducts following increasing MR signaling. This enhances visibility of cyst-duct communications. This can help distinguish IPMN from other cystic lesions [68].

Conventional imaging studies, including CT and MRI, contain a huge amount of data, which are currently not used systematically to enhance information. Study of these granular and comprehensive datasets is defined as ‘radiomics’. Radiomics has potential to enhance diagnostic strategies and prognostication in a personalized medicine approach [69]. It utilizes quantitative image analysis to extract features in conjunction with machine learning and artificial intelligence (AI) methods like

supporting vector machines, random forest, and convolutional neural network for feature selection and classification. Selected features can then serve as imaging biomarkers to predict high-risk pancreatic cystic lesions which has been demonstrated in some studies [70–72].

Needle-based confocal laser endomicroscopy can be used during EUS-FNA which allows observation of the inner wall of the cyst in microscopic detail. This technique has shown promising results in differentiation of PCN and performed better than EUS + CEA alone [73]. The sensitivities and specificities of needle-based confocal laser endomicroscopy for the diagnosis of serous cystadenoma, mucinous PCL, and premalignant PCL were ≥95% [73].

EUS guided through-the-needle biopsy is a recently developed technique where a microforceps is passed through a standard FNA needle to obtain a biopsy of the cyst wall or mural nodules. EUS with through-the-needle biopsy technique provided better results in diagnosing mucinous cysts than CEA and FNA cytology [74].

Cyst fluid analysis is a developing field and likely will be of increased importance in the future, particularly the use of next generation sequencing methods [75–78]. Investigators have reported *KRAS*/*GNAS* mutations to be present in 100% of IPMN [76], and to be highly sensitive and specific (89% and 100% respectively) for IPMN and mucinous cystic lesions [76]. Additional *TP53*/*PIK3CA*/*PTEN* evaluation provided an 88% sensitivity and 97% specificity for IPMN with advanced neoplastic changes [76]. VHL mutations and deletions are associated with SCN [46, 79].

Since no single marker or feature of any test provides perfect accuracy, the added value of several modalities may hold a better clue to optimal risk stratification. The *CompCyst* test is based on combination of selected clinical features, imaging characteristics, and cyst fluid genetic and biochemical markers [80]. Using data from 436 patients with pancreatic cysts, a Johns Hopkins-led collaboration used *CompCyst* to classify patients into those who require surgery, those who should be monitored, and those who do not require further surveillance. The investigators validated the *CompCyst* in an independent cohort of 426 patients, with histopathology used as the gold standard. The *CompCyst* test was more accurate than the management dictated by conventional clinical and imaging criteria alone [80]. Indeed, the *CompCyst* test would have made surgery unnecessary in >50% of patients and might have the potential to reduce morbidity of surgery and economic costs. Of note, the study was limited by using patients with cysts who underwent resection, therefore prospective validation is needed.

50.8 Management of Pancreatic Cysts

Surgical resection of a PCN is recommended where the risk of malignant transformation outweighs the risk associated with surgery, as mentioned for separate cystic lesions above. Type and extent of surgery may depend on the type and location of the cyst in the pancreatic gland (Fig. 50.6).

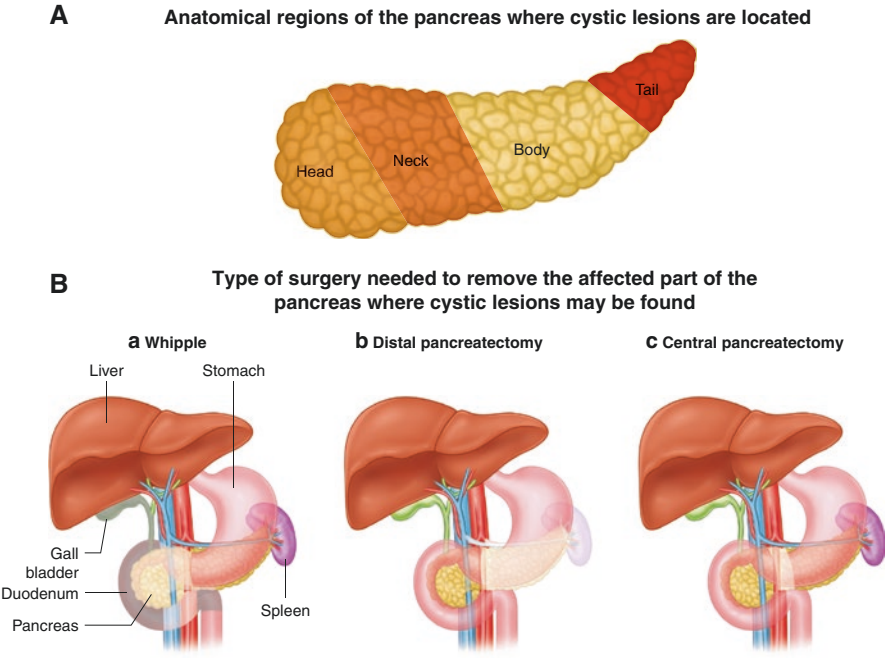


Fig. 50.6 Location of cysts and type of resection considered for pancreatic cysts. (**A**) Locations of cysts within the pancreatic gland; the neck is over the porto-mesenteric confluence. (**B**) types of resections considered in cystic lesions, (a) pancreatoduodenectomy, (b) distal pancreatectomy and (c) central pancreatectomy

In general, IPMN with high risk features and MCN have malignant potential and should be considered for surgery, but also other lesions may be resected as the best strategy. Obviously, the need for resection over surveillance should be viewed in light of patient age, comorbidity and preference and carefully balanced against the risk of progression to invasive malignancy. All guidelines recommend that surgery should be performed in high volume centers after consultation in multidisciplinary teams.

If the cyst is located in the head or uncinate process a pancreatoduodenectomy is performed, while a distal pancreatectomy is performed for cysts in the body or tail. Parenchymal sparing resection and enucleations are sometimes indicated, but as yet there is no solid data to guide decisions in the context of cystic lesions. Although some institutions employ this strategy for small IPMN this is not widely accepted. Total pancreatectomy, sometimes indicated for disease affecting the entire gland, needs careful consideration as risk and the long-term consequences are considerable [81].

According to the European [19] and IAP guidelines [18] resection is indicated in all SPN as long as the patient is fit for surgery. Cystic pancreatic neuroendocrine tumours should be resected if they are symptomatic, if there are signs of malignant behaviour or if size exceeds >20 mm as there is a 20% risk of malignancy [19].

Smaller asymptomatic cysts without any sign of malignancy can be surveilled [19]. The IAP guidelines [18] recommend resection for all MCN, while the European guidelines [19] recommend resection only if the size is >40 mm, an enhancing mural nodule is detected or if symptoms occur. Guidelines for IPMN are mentioned in a separate chapter in this book.

As current surgical treatment options pose a significant risk of morbidity and mortality, hence the development of efficacious minimally invasive treatment options would be desirable. Pancreatic cyst ablation is one such technique which is showing promising potential.

Ethanol ablation used in early trials showed disappointing efficacy and a significant risk of pancreatitis [82]. A recent development is cyst lavage with ethanol followed by infusion of the chemotherapeutic agent paclitaxel. A successful ablation rate of 50–79% was observed, but with significant risk of developing pancreatitis, peritonitis and venous thrombosis in up to 10% of patients [82]. A more recent study showed the same ablation effect with significantly less side effects when chemotherapeutic ablation was used alone [82, 83].

Studies comparing chemical ablation with surgery or surveillance are lacking, therefore no recommendations can be made at this point of time. Trials are also ongoing evaluating the effect of EUS guided radiofrequency ablation, the results still pending.

50.9 Conclusion

Pancreatic cystic lesions vary from benign to premalignant lesions requiring resection and are becoming discovered at an increasing rate due to the increasing prevalence of high-quality radiologic imaging. Guidelines developed in the last decades help in the treatment decision, but there is still ongoing debate concerning appropriate selection for surgery or continued observation in individual patients due to the potential morbidity traditionally associated with resections. However new advances in diagnostic accuracy through radiology and EUS procedures will likely improve patient selection, and advances in endoscopy and minimally invasive surgery will reduce their complications. Molecular biomarkers may prove beneficial in selecting high risk candidates for progression or facilitate intervals of surveillance.

References

1. Farrell JJ. Prevalence, diagnosis and management of pancreatic cystic neoplasms: current status and future directions. Gut Liver. 2015;9(5):571–89. https://doi.org/10.5009/gnl15063.
2. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8(9):806–11. https://doi.org/10.1016/j.cgh.2010.05.017.

3. Zerboni G, Signoretti M, Crippa S, Falconi M, Arcidiacono PG, Capurso G. Systematic review and meta-analysis: prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals. Pancreatology. 2019;19(1):2–9. https://doi.org/10.1016/j.pan.2018.11.014.
4. Stutchfield BM, Nayar M, Penman ID. Pancreatic cystic lesions: risk stratification and management based on recent guidelines. Frontline Gastroenterol. 2019;10(2):182–7. https://doi.org/10.1136/flgastro-2018-101076.
5. van Huijgevoort NCM, Del Chiaro M, Wolfgang CL, van Hooft JE, Besselink MG. Diagnosis and management of pancreatic cystic neoplasms: current evidence and guidelines. Nat Rev Gastroenterol Hepatol. 2019; https://doi.org/10.1038/s41575-019-0195-x.
6. Perri G, Marchegiani G, Frigerio I, Dervenis CG, Conlon KC, Bassi C, et al. Management of pancreatic cystic lesions. Dig Surg. 2019:1–9. https://doi.org/10.1159/000496509.
7. Brewer Gutierrez OI, Lennon AM. Pancreatic cysts: sinister findings or incidentalomas? Med Clin North Am. 2019;103(1):163–72. https://doi.org/10.1016/j.mcna.2018.08.004.
8. Aunan JR, Jamieson NB, Soreide K. Observation or resection of pancreatic intraductal papillary mucinous neoplasm: an ongoing tug of war. World J Gastrointest Oncol. 2019;11(12):1092–100. https://doi.org/10.4251/wjgo.v11.i12.1092.
9. Scholten L, van Huijgevoort NCM, van Hooft JE, Besselink MG, Del Chiaro M. Pancreatic cystic neoplasms: different types, different management, new guidelines. Visc Med. 2018;34(3):173–7. https://doi.org/10.1159/000489641.
10. Hasan A, Visrodia K, Farrell JJ, Gonda TA. Overview and comparison of guidelines for management of pancreatic cystic neoplasms. World J Gastroenterol. 2019;25(31):4405–13. https://doi.org/10.3748/wjg.v25.i31.4405.
11. Vilas-Boas F, Macedo G. Management guidelines for pancreatic cystic lesions: should we adopt or adapt the current roadmaps? J Gastrointestin Liver Dis. 2019;28(4):495–501. https://doi.org/10.15403/jgld-341.
12. Perri G, Marchegiani G, Frigerio I, Dervenis CG, Conlon KC, Bassi C, et al. Management of pancreatic cystic lesions. Dig Surg. 2019; https://doi.org/10.1159/000496509.
13. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2019; https://doi.org/10.1111/his.13975.
14. Cho CS, Russ AJ, Loeffler AG, Rettammel RJ, Oudheusden G, Winslow ER, et al. Preoperative classification of pancreatic cystic neoplasms: the clinical significance of diagnostic inaccuracy. Ann Surg Oncol. 2013;20(9):3112–9. https://doi.org/10.1245/s10434-013-2986-6.
15. Del Chiaro M, Segersvard R, Pozzi Mucelli R, Rangelova E, Kartalis N, Ansorge C, et al. Comparison of preoperative conference-based diagnosis with histology of cystic tumors of the pancreas. Ann Surg Oncol. 2014;21(5):1539–44. https://doi.org/10.1245/s10434-013-3465-9.
16. Salvia R, Malleo G, Marchegiani G, Pennacchio S, Paiella S, Paini M, et al. Pancreatic resections for cystic neoplasms: from the surgeon's presumption to the pathologist's reality. Surgery. 2012;152(3 Suppl 1):S135–42. https://doi.org/10.1016/j.surg.2012.05.019.
17. Munigala S, Gelrud A, Agarwal B. Risk of pancreatic cancer in patients with pancreatic cyst. Gastrointest Endosc. 2016;84(1):81–6. https://doi.org/10.1016/j.gie.2015.10.030.
18. Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17(5):738–53. https://doi.org/10.1016/j.pan.2017.07.007.
19. Del Chiaro M, Besselink M, Scholten L, Bruno MJ, Cahen DL, Gress TM, et al. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67(5):789. https://doi.org/10.1136/gutjnl-2018-316027.
20. Vege SS, Ziring B, Jain R, Moayyedi P, Adams MA, Dorn SD, et al. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4):819–22. https://doi.org/10.1053/j.gastro.2015.01.015.

21. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018;113(4):464–79. https://doi.org/10.1038/ajg.2018.14.
22. Megibow AJ, Baker ME, Morgan DE, Kamel IR, Sahani DV, Newman E, et al. Management of incidental pancreatic cysts: a white paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14(7):911–23. https://doi.org/10.1016/j.jacr.2017.03.010.
23. Levink IJM, Bruno MJ, Cahen DL. Management of intraductal papillary mucinous neoplasms: controversies in guidelines and future perspectives. Curr Treat Options Gastroenterol. 2018;16(3):316–32. https://doi.org/10.1007/s11938-018-0190-2.
24. Groot VP, Thakker SS, Gemenetzis G, Noe M, Javed AA, Burkhart RA, et al. Lessons learned from 29 lymphoepithelial cysts of the pancreas: institutional experience and review of the literature. HPB (Oxford). 2018;20(7):612–20. https://doi.org/10.1016/j.hpb.2018.01.003.
25. Dziri C, Dougaz W, Bouasker I. Surgery of the pancreatic cystic echinococcosis: systematic review. Transl Gastroenterol Hepatol. 2017;2:105. https://doi.org/10.21037/tgh.2017.11.13.
26. Lada PE, Termengo D, Caceres G, Sanchez Tacone C, Caballero F, Sonzini AP. Primary hydatid cyst of the pancreas. Rev Fac Cien Med Univ Nac Cordoba. 2017;74(1):33–6.
27. Dong J, Klair JS, El-Abiad R. What did I just aspirate? Rare pancreatic cyst. Gastrointest Endosc. 2019;90(1):164–5. https://doi.org/10.1016/j.gie.2019.03.004.
28. Chen Q, Xia J. A giant hemolymphangioma of the pancreas: a case report and literature review. Medicine (Baltimore). 2018;97(41):e12599. https://doi.org/10.1097/md.0000000000012599.
29. Shahid M, Javed Z, Usman M, Iltaf S. True congenital pancreatic cyst: a rare entity. Cureus. 2018;10(9):e3318. https://doi.org/10.7759/cureus.3318.
30. van der Naald N, Engelsman AF, Engelbrecht MRW, Verheij J, Besselink MG, Busch OR, et al. Tuberculosis presenting as a pancreatic cystic neoplasm. BMJ Case Rep. 2018;11(1) https://doi.org/10.1136/bcr-2018-225983.
31. Habashi S, Draganov PV. Pancreatic pseudocyst. World J Gastroenterol. 2009;15(1):38–47. https://doi.org/10.3748/wjg.15.38.
32. Sheu Y, Furlan A, Almusa O, Papachristou G, Bae KT. The revised Atlanta classification for acute pancreatitis: a CT imaging guide for radiologists. Emerg Radiol. 2012;19(3):237–43. https://doi.org/10.1007/s10140-011-1001-4.
33. Aghdassi AA, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Pancreatic pseudocysts—when and how to treat? HPB. 2006;8(6):432–41. https://doi.org/10.1080/13651820600748012.
34. Tyberg A, Karia K, Gabr M, Desai A, Doshi R, Gaidhane M, et al. Management of pancreatic fluid collections: a comprehensive review of the literature. World J Gastroenterol. 2016;22(7):2256–70. https://doi.org/10.3748/wjg.v22.i7.2256.
35. Assifi MM, Nguyen PD, Agrawal N, Dedania N, Kennedy EP, Sauter PK, et al. Non-neoplastic epithelial cysts of the pancreas: a rare, benign entity. J Gastrointest Surg. 2014;18(3):523–31. https://doi.org/10.1007/s11605-014-2459-7.
36. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1–2):17–32. https://doi.org/10.1159/000090023.
37. Tanaka M, Fernandez-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97. https://doi.org/10.1016/j.pan.2012.04.004.
38. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17(5):738–53. https://doi.org/10.1016/j.pan.2017.07.007.
39. Crippa S, Salvia R, Warshaw AL, Domínguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247(4):571–9. https://doi.org/10.1097/SLA.0b013e31811f4449.
40. Ngamruengphong S, Lennon AM. Analysis of pancreatic cyst fluid. Surg Pathol Clin. 2016;9(4):677–84. https://doi.org/10.1016/j.path.2016.05.010.

41. Del Chiaro M, Verbeke C, Salvia R, Kloppel G, Werner J, McKay C, et al. European experts consensus statement on cystic tumours of the pancreas. Digest Liver Dis. 2013;45(9):703–11. https://doi.org/10.1016/j.dld.2013.01.010.
42. Keane MG, Shamali A, Nilsson LN, Antila A, Millastre Bocos J, Marijinissen Van Zanten M, et al. Risk of malignancy in resected pancreatic mucinous cystic neoplasms. Br J Surg. 2018;105(4):439–46. https://doi.org/10.1002/bjs.10787.
43. Jais B, Rebours V, Malleo G, Salvia R, Fontana M, Maggino L, et al. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). Gut. 2016;65(2):305–12. https://doi.org/10.1136/gutjnl-2015-309638.
44. Huh J, Byun JH, Hong S-M, Kim KW, Kim JH, Lee SS, et al. Malignant pancreatic serous cystic neoplasms: systematic review with a new case. BMC Gastroenterol. 2016;16(1):97. https://doi.org/10.1186/s12876-016-0518-0.
45. Strobel O, Z'Graggen K, Schmitz-Winnenthal FH, Friess H, Kappeler A, Zimmermann A, et al. Risk of malignancy in serous cystic neoplasms of the pancreas. Digestion. 2003;68(1):24–33. https://doi.org/10.1159/000073222.
46. Charville GW, Kao C-S. Serous neoplasms of the pancreas: a comprehensive review. Arch Pathol Lab Med. 2018;142(9):1134–40. https://doi.org/10.5858/arpa.2017-0195-RS.
47. El Nakeeb A, Abdel Wahab M, Elkashef WF, Azer M, Kandil T. Solid pseudopapillary tumour of the pancreas: incidence, prognosis and outcome of surgery (single center experience). Int J Surg. 2013;11(6):447–57. https://doi.org/10.1016/j.ijsu.2013.04.009.
48. Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, et al. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? Pancreas. 2014;43(3):331–7. https://doi.org/10.1097/mpa.0000000000000061.
49. Tipton SG, Smyrk TC, Sarr MG, Thompson GB. Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg. 2006;93(6):733–7. https://doi.org/10.1002/bjs.5334.
50. Wright MJ, Javed AA, Saunders T, Zhu Y, Burkhart RA, Yu J, et al. Surgical resection of 78 pancreatic solid pseudopapillary tumors: a 30-year single institutional experience. J Gastrointest Surg. 2019; https://doi.org/10.1007/s11605-019-04252-7.
51. Tjaden C, Hassenpflug M, Hinz U, Klaiber U, Klauss M, Buchler MW, et al. Outcome and prognosis after pancreatectomy in patients with solid pseudopapillary neoplasms. Pancreatology. 2019;19(5):699–709. https://doi.org/10.1016/j.pan.2019.06.008.
52. Sanhueza CT, Huffman BM, Jin Z, Hartgers ML, Smyrk TC, Westin G, et al. Solid pseudopapillary neoplasms of the pancreas: a large american cohort. Pancreas. 2019;48(4):e21–e2. https://doi.org/10.1097/mpa.0000000000001288.
53. Liu M, Liu J, Hu Q, Xu W, Liu W, Zhang Z, et al. Management of solid pseudopapillary neoplasms of pancreas: a single center experience of 243 consecutive patients. Pancreatology. 2019;19(5):681–5. https://doi.org/10.1016/j.pan.2019.07.001.
54. Hansen CP, Kristensen TS, Storkholm JH, Federspiel BH. Solid pseudopapillary neoplasm of the pancreas: clinical-pathological features and management, a single-center experience. Rare Tumors. 2019;11:2036361319878513. https://doi.org/10.1177/2036361319878513.
55. Nguyen NQ, Johns AL, Gill AJ, Ring N, Chang DK, Clarkson A, et al. Clinical and immunohistochemical features of 34 solid pseudopapillary tumors of the pancreas. J Gastroenterol Hepatol. 2011;26(2):267–74. https://doi.org/10.1111/j.1440-1746.2010.06466.x.
56. Basar O, Brugge WR. My treatment approach: pancreatic cysts. Mayo Clin Proc. 2017;92(10):1519–31. https://doi.org/10.1016/j.mayocp.2017.06.017.
57. Heiser PW, Cano DA, Landsman L, Kim GE, Kench JG, Klimstra DS, et al. Stabilization of beta-catenin induces pancreas tumor formation. Gastroenterology. 2008;135(4):1288–300. https://doi.org/10.1053/j.gastro.2008.06.089.
58. Hao EIU, Hwang HK, Yoon DS, Lee WJ, Kang CM. Aggressiveness of solid pseudopapillary neoplasm of the pancreas: a literature review and meta-analysis. Medicine (Baltimore). 2018;97(49):e13147. https://doi.org/10.1097/md.0000000000013147.

59. Zou C, Yang F, Fu D. Meta-analysis of Ki-67 expression for recurrence in patients with solid pseudopapillary tumor of the pancreas. HPB (Oxford). 2019; https://doi.org/10.1016/j.hpb.2019.09.018.
60. Singhi AD, Chu LC, Tatsas AD, Shi C, Ellison TA, Fishman EK, et al. Cystic pancreatic neuroendocrine tumors: a clinicopathologic study. Am J Surg Pathol. 2012;36(11):1666–73. https://doi.org/10.1097/PAS.0b013e31826a0048.
61. Westerveld D, Goddard A, Harris N, Khullar V, Forde J, Draganov PV, et al. Survey study on the practice patterns of the evaluation and management of incidental pancreatic cysts. Dig Dis Sci. 2019;64(3):689–97. https://doi.org/10.1007/s10620-018-5368-x.
62. Kamata K, Kitano M, Omoto S, Kadosaka K, Miyata T, Yamao K, et al. Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of pancreatic cysts. Endoscopy. 2016;48(1):35–41. https://doi.org/10.1055/s-0034-1393564.
63. Yamamoto N, Kato H, Tomoda T, Matsumoto K, Sakakihara I, Noma Y, et al. Contrast-enhanced harmonic endoscopic ultrasonography with time-intensity curve analysis for intraductal papillary mucinous neoplasms of the pancreas. Endoscopy. 2016;48(1):26–34. https://doi.org/10.1055/s-0034-1393563.
64. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, et al. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology. 2015;149(6):1501–10. https://doi.org/10.1053/j.gastro.2015.07.041.
65. Kanda M, Knight S, Topazian M, Syngal S, Farrell J, Lee J, et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 2013;62(7):1024–33. https://doi.org/10.1136/gutjnl-2012-302823.
66. Lariño-Noia J, Iglesias-Garcia J, de la Iglesia-Garcia D, Dominguez-Muñoz JE. EUS-FNA in cystic pancreatic lesions: where are we now and where are we headed in the future? Endosc Ultrasound. 2018;7(2):102–9. https://doi.org/10.4103/eus.eus_93_17.
67. Chang Y-T, Tung C-C, Chang M-C, Wu C-H, Chen B-B, Jan IS. Age and cystic size are associated with clinical impact of endoscopic ultrasonography-guided fine-needle aspiration on the management of pancreatic cystic neoplasms. Scand J Gastroenterol. 2019;54(4):506–12. https://doi.org/10.1080/00365521.2019.1601254.
68. Boraschi P, Donati F, Cervelli R, Pacciardi F. Secretin-stimulated MR cholangiopancreatography: spectrum of findings in pancreatic diseases. Insights Imaging. 2016;7(6):819–29. https://doi.org/10.1007/s13244-016-0517-2.
69. Dalal V, Carmicheal J, Dhaliwal A, Jain M, Kaur S, Batra SK. Radiomics in stratification of pancreatic cystic lesions: machine learning in action. Cancer Lett. 2020;469:228–37. https://doi.org/10.1016/j.canlet.2019.10.023.
70. Chakraborty J, Midya A, Gazit L, Attiyeh M, Langdon-Embry L, Allen PJ, et al. CT radiomics to predict high-risk intraductal papillary mucinous neoplasms of the pancreas. Med Phys. 2018;45(11):5019–29. https://doi.org/10.1002/mp.13159.
71. Hanania AN, Bantis LE, Feng Z, Wang H, Tamm EP, Katz MH, et al. Quantitative imaging to evaluate malignant potential of IPMNs. Oncotarget. 2016;7(52):85776–84. https://doi.org/10.18632/oncotarget.11769.
72. Cheng SH, Liu D, Hou B, Hu Y, Huo L, Xing H, et al. PET-MR imaging and MR texture analysis in the diagnosis of pancreatic cysts: a prospective preliminary study. Acad Radiol. 2019; https://doi.org/10.1016/j.acra.2019.09.001.
73. Napoleon B, Palazzo M, Lemaistre AI, Caillol F, Palazzo L, Aubert A, et al. Needle-based confocal laser endomicroscopy of pancreatic cystic lesions: a prospective multicenter validation study in patients with definite diagnosis. Endoscopy. 2019;51(9):825–35. https://doi.org/10.1055/a-0732-5356.
74. Yang D, Samarasena JB, Jamil LH, Chang KJ, Lee D, Ona MA, et al. Endoscopic ultrasound-guided through-the-needle microforceps biopsy in the evaluation of pancreatic cystic lesions: a multicenter study. Endoscopy Int Open. 2018;6(12):E1423–e30. https://doi.org/10.1055/a-0770-2700.
75. Volckmar AL, Endris V, Gaida MM, Leichsenring J, Stogbauer F, Allgauer M, et al. Next generation sequencing of the cellular and liquid fraction of pancreatic cyst fluid supports dis-

crimination of IPMN from pseudocysts and reveals cases with multiple mutated driver clones: first findings from the prospective ZYSTEUS biomarker study. Genes Chromosomes Cancer. 2019;58(1):3–11. https://doi.org/10.1002/gcc.22682.
76. Singhi AD, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, et al. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. Gut. 2018;67(12):2131–41. https://doi.org/10.1136/gutjnl-2016-313586.
77. Rosenbaum MW, Jones M, Dudley JC, Le LP, Iafrate AJ, Pitman MB. Next-generation sequencing adds value to the preoperative diagnosis of pancreatic cysts. Cancer Cytopathol. 2017;125(1):41–7. https://doi.org/10.1002/cncy.21775.
78. Wang J, Paris PL, Chen J, Ngo V, Yao H, Frazier ML, et al. Next generation sequencing of pancreatic cyst fluid microRNAs from low grade-benign and high grade-invasive lesions. Cancer Lett. 2015;356(2 Pt B):404–9. https://doi.org/10.1016/j.canlet.2014.09.029.
79. Wu J, Jiao Y, Dal Molin M, Maitra A, de Wilde RF, Wood LD, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc Natl Acad Sci U S A. 2011;108(52):21188–93. https://doi.org/10.1073/pnas.1118046108.
80. Springer S, Masica DL, Dal Molin M, Douville C, Thoburn CJ, Afsari B, et al. A multimodality test to guide the management of patients with a pancreatic cyst. Sci Transl Med. 2019;11(501) https://doi.org/10.1126/scitranslmed.aav4772.
81. Pulvirenti A, Pea A, Rezaee N, Gasparini C, Malleo G, Weiss MJ, et al. Perioperative outcomes and long-term quality of life after total pancreatectomy. Br J Surg. 2019; https://doi.org/10.1002/bjs.11185.
82. Moyer MT, Maranki JL, DeWitt JM. EUS-guided pancreatic cyst ablation: a clinical and technical review. Curr Gastroenterol Rep. 2019;21(5):19. https://doi.org/10.1007/s11894-019-0686-5.
83. Moyer MT, Sharzehi S, Mathew A, Levenick JM, Headlee BD, Blandford JT, et al. The safety and efficacy of an alcohol-free pancreatic cyst ablation protocol. Gastroenterology. 2017;153(5):1295–303. https://doi.org/10.1053/j.gastro.2017.08.009.

Chapter 51
EUS and Solid Pancreatic Lesions

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Take Home Messages

- EUS has a higher diagnostic accuracy than all other cross-sectional imaging modalities for the detection of solid pancreatic lesions below 30 mm.
- EUS guided sampling of a solid pancreatic lesion is a first-line approach in case tissue diagnosis is required.
- EUS is used as a supplement to CT for assessing resectability of pancreatic cancer but there is no recommendation for routine EUS performance in patients with pancreatic cancer found to have resectable disease on CT scan.

Pearls and Pitfalls

- Ancillary techniques, such as contrast-enhanced EUS and real time elastography, may help characterize a solid pancreatic lesion and select patients to undergo EUS-guided sampling, thus potentially improving diagnostic accuracy.
- Fine needle biopsy (FNB) provides the possibility to obtain histologically intact samples, potentially leading to specific histopathology diagnosis and adequate specimens for immunohistochemical analysis and molecular profiling.
- EUS performance is highly operator dependent.

Future Perspectives

- Further studies are needed in order to establish the role, long term efficacy, and survival benefit of EUS guided therapies in the management of pancreatic adenocarcinoma.
- Larger prospective studies are needed to confirm the accuracy of EUS-FNB to provide a specific diagnosis even in non-malignant cases of solid pancreatic lesions.

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51.1 Introduction

In contrast with pancreatic cystic lesions which are commonly detected as incidental findings in imaging examinations, patients diagnosed with solid pancreatic lesions (SPLs) most frequently present with symptoms such as jaundice and epigastric pain. Endoscopic ultrasound (EUS) plays a crucial role when a SPL is suspected, as it may provide high-resolution images of the pancreas through the stomach and duodenum, without the disruption of intervening gas, fat, and bone. Consequently EUS provides exceptional accuracy for the detection of pancreatic focal lesions, especially in patients with small tumors of 3 cm or less with a median sensitivity of 94% [1]. After initial assessment, EUS-guided fine needle aspiration (FNA) or fine needle biopsy (FNB), potentially in combination with ancillary techniques such as contrast enhancement and elastography, may help obtain a specific diagnosis [1]. Furthermore, since most SPLs turn out to be pancreatic cancer, EUS may provide information on staging and resectability, which are important parameters for further management decisions, including surgical or EUS-guided therapy.

The aim of this chapter is to describe the utility of EUS in the management of solid pancreatic lesions with special reference to its role in their detection, sampling, and staging as well as EUS-guided endotherapy.

51.2 Endoscopic Ultrasound Examination

EUS is an endoscopic exam in which an ultrasound probe is fitted at the tip of the endoscope enabling the operator to obtain high-resolution images of the pancreas through the stomach and duodenum, by transducing high-frequency sound waves. EUS scopes can be either radial or linear, with the former providing a circumferential (usually 360°) view of the area whereas in the latter views are in the same line with the scope shaft, compulsory for real-time EUS-guided FNA performance (Fig. 51.1).

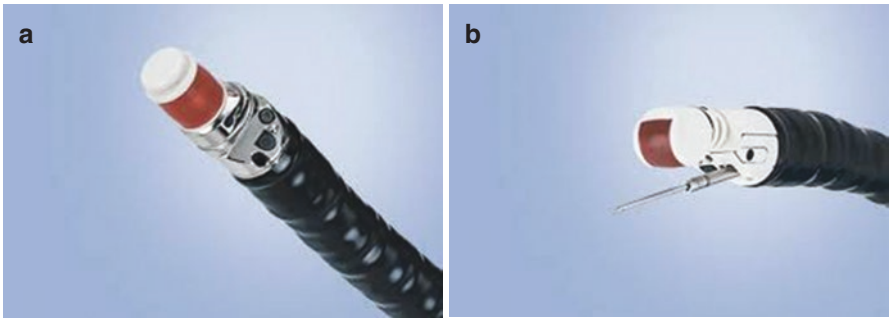

Fig. 51.1 (**a**) Tip of a radial echoendoscope. It bears an ultrasound probe which may scan a 360° plane vertical to the shaft of the echoendoscope. (**b**) Tip of a linear array echoendoscope. It bears an ultrasound probe which may scan an axe-like plane parallel to the shaft of the echoendoscope, enabling real-time visualization of aspiration/biopsy needles (Courtesy of Olympus Corp)

Similar to conventional upper gastrointestinal (GI) endoscopy patients typically undergo a fasting period of at least 6 h for solids and 2–4 h for liquids [2]. Prior to starting the procedure, patients are placed in left lateral decubitus position [3]. However, EUS lasts usually longer and may be more inconvenient for the patient (due to the need of contact between the scope tip and the GI wall to establish acoustic coupling) compared to conventional upper GI endoscopy. Also, an EUS exam may be combined with interventional procedures (e.g. fine needle sampling). Consequently regarding sedation, ideally anesthesia provider assistance should be considered to accomplish deep sedation. This is associated with improved outcomes and better efficacy regarding EUS-FNA. However, under certain circumstances (including but not limited to national and local regulations and policies, patient comorbid illness burden, etc.) moderate sedation could be also administered and monitored by the echoendoscopist [4].

51.3 Detection of Solid Pancreatic Lesions

Although pancreatic adenocarcinoma accounts for the majority of SPLs, reaching 85%, several alternative diagnoses need to be considered including benign conditions, such as focal or IgG4-related autoimmune pancreatitis (Table 51.1). The distinction is important as appropriate therapy may vary significantly among different conditions [5–9].

According to a recent meta-analysis [1], EUS is the most sensitive imaging modality for the detection of pancreatic lesions with a median sensitivity of 94%. Compared with computed tomography (CT) or transabdominal ultrasound scans, EUS has higher sensitivity (74% vs. 98% and 67% vs. 94%, respectively) [1]. There are only few comparative studies between EUS and magnetic resonance imaging (MRI), showing higher sensitivity for the detection of pancreatic lesions in the case of the former (98% vs. 87.5%) [10]. Moreover its negative predictive value reaches

Table 51.1 Differential diagnosis of solid pancreatic lesions

Neoplastic	Non neoplastic
Pancreatic adenocarcinoma (85%)	Chronic pancreatitis
Neuroendocrine tumor (<10%)	Autoimmune pancreatitis
Metastasis[a] (2–5%)	Teratoma
Primary pancreatic lymphoma (0.5%)	Ectopic spleen
Solid pseudopapillary tumors	Sarcoidosis
Ampullary tumor	Hamartoma
Acinar cell carcinoma	Lymphoid hyperplasia
Pancreatoblastoma	Lipomatous pseudohypertrophy
	Lymphangioma
	Lymphoepithelial cyst
	Endometriosis

[a]Mainly from breast carcinoma, lung carcinoma, melanoma, gastrinoma, renal cell carcinoma, retroperitoneal liposarcoma, osteosarcoma, GI tract carcinoma

Table 51.2 Detection efficacy of EUS compared with CT and MRI according to different SPL size [12]

	EUS (sensitivity %)	CT (sensitivity %)	MRI (sensitivity %)
SPL < 3 cm	93	53	67
SPL < 2 cm	94	50	–
SPL < 1 cm	80	33–75	–

100%, with the few false negative cases being related to the presence of chronic pancreatitis, diffuse carcinoma, or recent acute pancreatitis [11].

EUS demonstrates even better comparative diagnostic efficacy in the detection of small lesions below 30 mm [1] .The difference in detection efficacy increases with decreasing SPL (Table 51.2) [12].

51.4 EUS-Guided Sampling of SPLs

51.4.1 EUS-FNA

Although EUS-FNA of SPLs has been shown to be as accurate as percutaneous (CT or US guided) or surgical approaches to obtain a tissue diagnosis [13], as regards to SPLs < 3 cm, EUS-FNA has greater accuracy than US- or CT-guided FNA ($p = 0.015$) [14]. This superiority in favor of EUS-FNA also applies to complication rates [15] and cost minimization [16].Thus, guidelines from all major endoscopy associations recommend EUS-guided sampling of an SPL as a first line approach in case tissue diagnosis is required [15] (Fig. 51.2). As an alternative, the percutaneous approach may be considered in metastatic disease [15]. In a meta-analysis including 41 studies (4766 patients), the sensitivity of EUS-FNA to detect the correct etiology for SPLs is 86.8% (95% confidence interval [CI], 85.5–87.9)with a specificity of 95.8% (95% CI, 94.6–96.7), a positive likelihood ratio of 15.2 (95% CI, 8.5–27.3) and a negative likelihood ratio of 0.17 (95% CI, 0.13–0.21) [17].

There are several technical and procedural parameters that can affect the diagnostic yield of EUS-FNA of pancreatic lesions [18, 19]. A recent network meta-analysis of 27 prospective randomized trials (2711 patients) found no difference in diagnostic accuracy between 25 and 22 G FNA needles for sampling SPLs (Relative Risk 1.03, 95% CI 0.91–1.17) [20]. The suction technique performed by applying negative pressure during aspiration yields higher cellularity (odds ratio [OR] 2.12; 95% CI, 1.37–3.30), accuracy (85.2% vs. 75.9%; $p = 0.004$), and sensitivity (82.4% vs. 72.1%; $p = 0.005$) when prospectively compared to no suction [21]. Additionally, the fanning technique is also utilized to acquire tissue by sampling multiple areas within a lesion during each pass. According to a randomized controlled trial with 54 patients the fanning technique showed better diagnostic accuracy when compared to standard approach (96.4% vs. 76.9%; $p = 0.05$). Fewer passes were required to

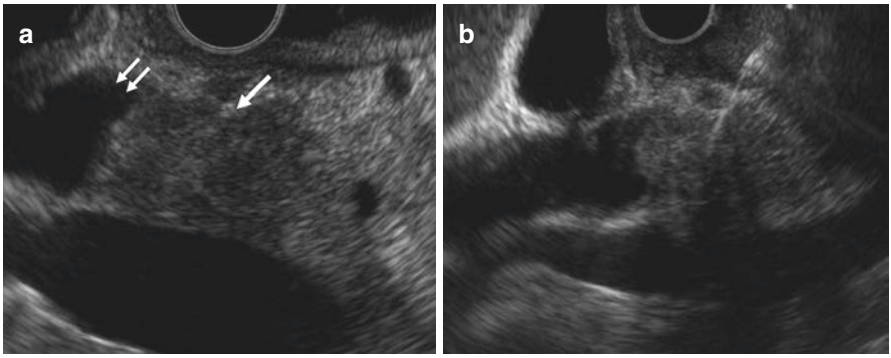

Fig. 51.2 (**a**) A hypoechoic lesion (arrow) in the head of the pancreas is seen obstructing the common bile duct (double arrow). (**b**) EUS-FNA obtained from the part of the lesion obstructing the common bile duct. A 25 G FNA needle is used

establish the diagnosis and in a significant proportion of patients it was achieved with just one pass (57.7% vs. 85.7%; $p = 0.02$) [22].

Rapid on-site evaluation (ROSE) of FNA specimens by a cytopathologist during EUS-guided sampling is considered an important factor improving specimen adequacy rate (average improvement by 10%, 95% CI 5–24%) [23], and diagnostic yield (increase by 10–30% from baseline) [18]. ROSE is also associated with fewer needle passes [24] and decrease in the number of repeated procedures by approximately 50% ($p = 0.024$) [25], but it may increase both procedural time and costs [24]. European Society of Gastrointestinal Endoscopy (ESGE) recommends EUS-guided sampling either without ROSE and 3–4 needle passes or with ROSE and individualized number of passes typically 2–3 [19].

51.4.2 EUS-FNB

Compared with FNA that usually provides only a cytopathology specimen, FNB needles usually also procure a tissue specimen (Fig. 51.3), with intact architecture allowing for immunohistochemical analysis and molecular profiling, leading to a diagnostic yield of >90% [26]. According to recent meta-analyses EUS-FNA and FNB share comparable safety and diagnostic accuracy rates provided FNA is accompanied by ROSE [20, 27], although FNB offers adequate specimens more frequently with fewer needle passes [27]. However, new generation FNB needles that have recently entered the market appear to have revolutionized the standard practice in tissue sampling. Their diagnostic adequacy on cellblock exceeds 90–95%, and their use is likely to obviate routine use of ROSE. Furthermore according to a prospective study with 30 patients who underwent both techniques, the accuracy for obtaining a specific tissue diagnosis, even in non-malignant cases, such

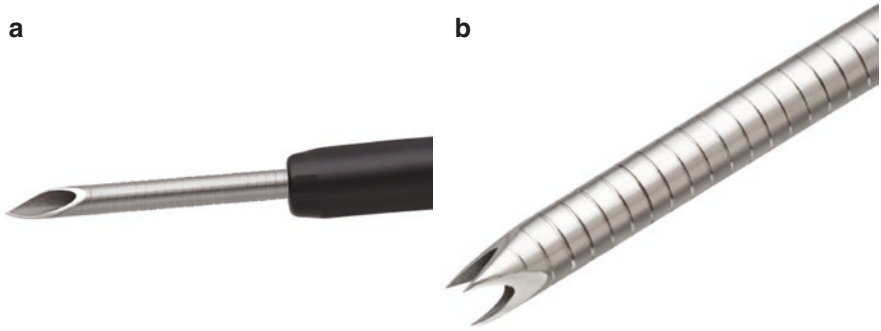

Fig. 51.3 (**a**) Tip of a standard 22 G FNA needle used for procurement of cytological aspirates. (**b**) Crown-shaped tip of a 22 G FNB needle used for histological core tissue acquisition (Courtesy of Boston Scientific)

as autoimmune or focal pancreatitis, was significantly higher for EUS-FNB compared with EUS-FNA (68.4% and 5.3%, $p < 0.005$) [28]. Should these findings be confirmed in larger prospective studies, it is conceivable that EUS-FNB may help avoid unnecessary surgery in patients with unclear diagnosis after a benign cytopathology sample (FNA), thus potentially reducing the number of patients with benign disease undergoing pancreatic resections due to presumed malignancy, and possibly provide a specific diagnosis of conditions that may be treated by medications, such as IgG4-related pancreatitis [29].

51.4.3 Sample Processing and Evaluation

Apart from conventional direct smears and liquid based cytology, cell block preparation is frequently applied aiming to optimize diagnostic accuracy (Table 51.3). Cell block is constructed by taking all or part of the pellet from the centrifuged liquid sample (specimen obtained by FNA in a liquid solution), forming a hardened structure and putting it into a paraffin wax block which is then processed as a histopathology specimen. It is superior to direct smear (or liquid-based cytology) demonstrating a higher sensitivity (85% vs. 61%; $p < 0.001$), negative predictive value (55% vs. 36%; $p = 0.046$), and accuracy (86.5% vs. 68%; $p < 0.001$) [30]. Combination of cytology smears and cell block techniques increases sensitivity from 79% to 90% ($p = 0.0313$) and accuracy from 81% to 91% ($p = 0.0313$) for diagnosing pancreatic malignancy compared to cytology smears alone [31]. This benefit of the cell block technique lays upon the advantage of performing ancillary (immunochemical and molecular) testing.

Table 51.3 Methods of specimen processing

Aspiration material	Biopsy-core tissue material
Direct smear cytology (dry, spray fixation, immersion into 95% alcohol) Liquid based cytology(saline, cell culture medium, fixative, formalin) Liquid samples → direct smear preparations Liquid samples → concentrate the material (cytospin technique, proprietary liquid-based cytology machine Liquid samples → cell block Possible visible tissue fragments or clots fixation for histology	Expel into fixative (fixed in formalin and processed in a paraffin wax block) for histology Expel onto glass slide for histology Expel into Saline for histology Cytologic evaluation of remaining specimen

51.5 Complications

The risk of complications of diagnostic EUS is generally low with a reported risk of perforation of 0.03–0.07%, and, in the event of FNA, bleeding of about 0.13% and acute pancreatitis of 1.5–2% [32]. Risk factors for the latter are higher number of punctures and more than 15 back and forth movements [33]. Tumor seeding is another potential adverse event of EUS-FNA and a matter of controversy in the literature [34]. Although there are case reports describing either peritoneal seeding, metastasis to the gastric wall or postoperative recurrence [35], there is no difference in survival or in recurrence risk between patients with vs. without previous EUS-guided sampling [36, 37]. Moreover, the risk of tumor seeding is regarded lower in the case of EUS-FNA compared to percutaneous sampling (2% vs. 16%) [38].

51.6 Image Enhancement Techniques

51.6.1 Real-Time Elastography (RE)

RE-EUS is a mean for real time evaluation of tissue stiffness and elasticity. Results are presented as transparent color images superimposed on the standard EUS gray scale images (Fig. 51.4). The technique is based on the principle of "the harder the lesion, the higher chance of malignancy" [39]. Important parameters are elasticity score and strain ratio (Table 51.4). Elasticity score alone is a rather subjective score. By combining both, a strain ratio value of 7.75 has been proposed as a cut-off to detect malignancy with a specificity of 95%, sensitivity of 99%, positive predictive value of 98%, negative predictive value of 98.5%, and accuracy of 97% [40].

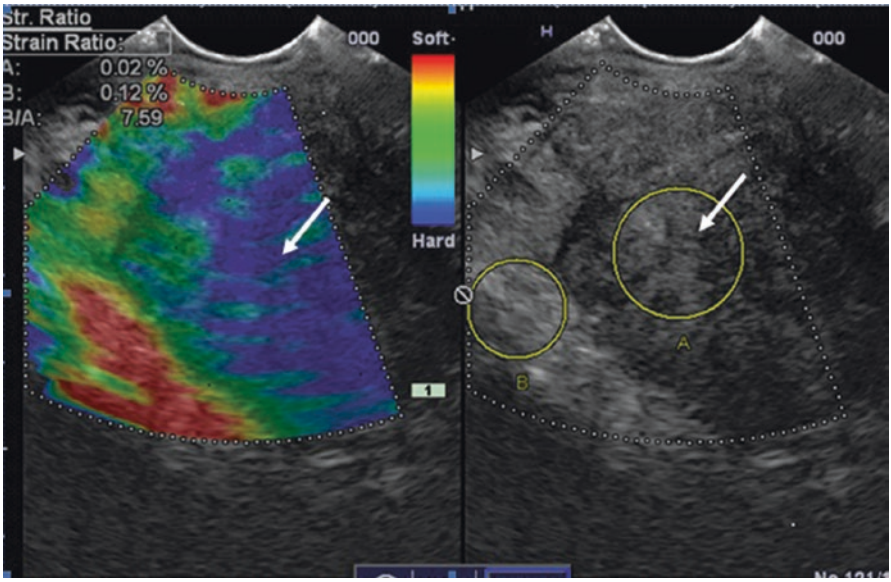

Fig. 51.4 Conventional EUS (right-hand side) and elastography image (left-hand side) of a hypoechoic mass lesion (arrow) in the pancreas. The lesion appears blue on strain elastography, indicating a hard lesion, compared to the surrounding parenchyma. The strain ratio is calculated taking into consideration a typical area of the lesion (**a**) and an area of the surrounding parenchyma (**b**). EUS-FNA showed adenocarcinoma (Courtesy of Dr. Roald Flesland Havre, University of Bergen, Norway)

Table 51.4 Classification system of elasticity for real-time elastography EUS [39]

Elasticity score	Stiffness	Possible histology
1	Homogeneous soft	Normal pancreatic tissue
2	Soft heterogenity	Fibrosis, chronic pancreatitis
3	Hard	Early pancreatic adenocarcinoma
4	Hard	Neuroendocrine tumor, metastasis
5	Hard	Advanced pancreatic adenocarcinoma

51.6.2 Contrast-Enhanced Harmonic (CEH) EUS

CEH-EUS is performed using power Doppler EUS after a bolus intravenous injection of micro-bubble agents (sulfur hexafluoride, galactose-palmitic acid or perfluorobutane) that generate an acoustic signal when hit by ultrasonic waves [41]. CEH-EUS allows the examination of the arterial and venous phases as well as of a potential wash-out effect. Pancreatic adenocarcinoma usually appears hypovascular in comparison with the surrounding pancreatic parenchyma whereas focal pancreatitis or pancreatic neuroendocrine tumors behave as iso- or hyper-vascular lesions, respectively (Fig. 51.5) [41]. A recent meta-analysis showed that CE-EUS has a high sensitivity of 0.92 (95%CI, 0.90–0.93) and a relatively high specificity of 0.86

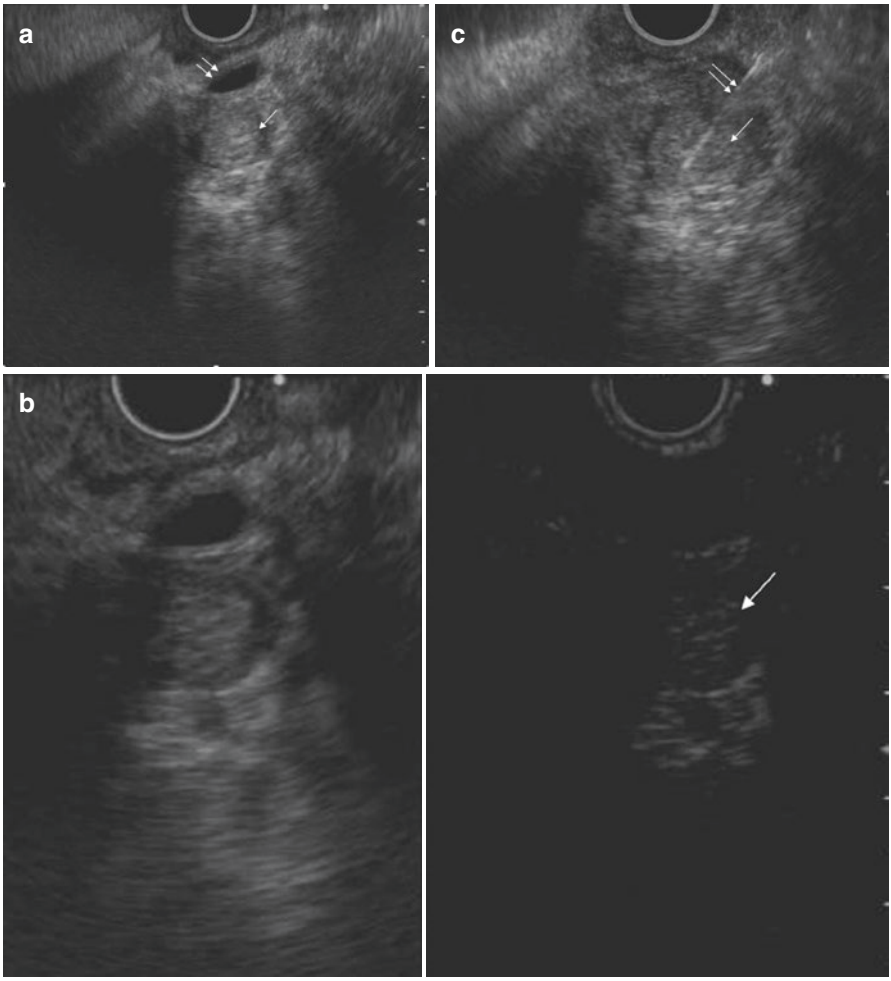

Fig. 51.5 (**a**) A hypoechoic filling defect without acoustic shadow seen in the distal pancreatic duct (arrow) in a patient referred due to unexplained relapsing pancreatitis. The distal common bile duct (double arrow) is seen as a structure with anechoic (black) lumen between the lesion in the pancreatic duct and the echoendoscope. (**b**) In order to discern viable tissue from debris 0.5 ml of SonoVue microbubble contrast medium was given iv. Uptake of contrast was seen in the lesion (arrow) in the right-hand side of the image, confirming that this was a solid lesion. (**c**) EUS-guided FNA of the lesion (arrow) using a 25 G FNA needle (double arrow)

(95% CI, 0.84–0.89) in the diagnosis of benign vs. malignant pancreatic tumors [42]. Besides enhancing SPL characterization, CEH-EUS is also useful for guiding FNA (highlighting vessels as well as necrotic and fibrotic parts to be avoided). According to a prospective cross-over study, CHE-EUS FNA offers numerically higher accuracy than conventional EUS-FNA (86% vs. 78%; ns), whereas by combining both methods the accuracy reaches 94% [41].

Both image enhancement techniques may be applied in patients with a negative FNA and a high suspicion of PC (especially in the background of chronic pancreatitis). Thus, in patients with a negative initial EUS-FNA, and characterization of a lesion as hard (RE-EUS) and hypovascular (CEH-EUS) or soft/mixed (RE-EUS) and hypervascular (CEH-EUS), the specificity to diagnose PC in the former and focal chronic pancreatitis in the latter is 100% with no reported false positive cases [43]. Since hard and hypovascular lesions are highly suggestive of PC and soft and hypervascular of benign focal pancreatitis, the use of FNA may be confined to indeterminate cases that account for 20% of patients (i.e. those with hard and hypervascular or soft/mixed and hypovascular lesions) [43].

Patients with chronic pancreatitis (CP) have a lifetime risk for PC around 13fold higher than that of general population [44] whereas in subsets of CP patients, this risk is even more pronounced (69-fold risk in hereditary pancreatitis and 100-fold risk in tropical pancreatitis) [44]. Data from a recent meta-analysis highlight the limited sensitivity for EUS-FNA to diagnose malignancy in a background of CP (54–74% vs. >90% in the absence of CP) [15, 45]. The supplemental use of both RTE-EUS and CEH-EUS, as described above may bridge the sensitivity gap and reduce false negative and false positive cases. However, larger prospective studies are warranted before RE-EUS and CEH-EUS are fully adopted in algorithms used in routine clinical practice.

51.7 Staging of Pancreatic Cancer

Accurate pre-operative staging of PC is important in order to be able to identify patients suitable for different therapeutic approaches: (1) resectable tumor that should be referred directly for potentially curative surgery; (2) locally advanced/borderline tumor that can be referred for downstaging therapy, and (3) metastatic/unresectable tumor that should be directed to palliative therapy.

In a meta-analysis, including 20 studies (726 patients), the estimated pooled sensitivity, specificity, and accuracy of EUS for staging pancreatic cancer, were 72%, 90%, and 90% for early and intermediate disease (T1 and T2), and 90%, 72%, and 90% for advanced disease (T3 and T4), respectively [46]. When compared with CT, four of five studies concluded that EUS was superior (25–73% vs. 63–85%) in terms of overall T stage accuracy [47].

Assessment of vascular invasion is part of T staging and is exceptionally crucial as it is related to resectability. It is defined by certain EUS criteria [48]. (Table 51.5).

Table 51.5 EUS criteria for vascular invasion

• Peripancreatic venous collaterals in an area of a mass that obliterates the normal anatomic location of a major vessel
• Tumor within the vessel lumen
• Abnormal vessel contour or irregular wall with loss of the vessel-parenchymal sonographic interface

According to a meta-analysis, the sensitivity to diagnose vascular invasion was higher for EUS (86%) than CT (58%), with comparable specificities (93% vs. 95%, respectively) [49]. This was confirmed by a systematic review involving 30 studies (1554 patients) reporting a diagnostic accuracy of 72% for EUS and 63%for CT [50]. EUS has a better performance specifically for venous (80–91%) compared to arterial invasion (17–67%) [49]. In the detection of portal vein or confluence invasion, the sensitivity of EUS is >80%, consistently superior to that of CT [1], increasing up to 100% when adding contrast [51]. Nevertheless, in the evaluation of the superior mesenteric vein, superior mesenteric artery, and celiac axis, the sensitivity of EUS decreases to 17–83%, 17%, and 50%, respectively [52].

51.7.1 Nodal Staging

Nodal evaluation includes perigastric, periduodenal, and celiac lymph nodes as well as nodes in the liver hilum. Mediastinal lymph nodes, distant to the primary tumor, should also be evaluated. Various EUS criteria have been suggested for the characterization of lymph nodes as malignant but those mostly used are round shape, hypoechogenicity, smooth border, and a short axis size greater than 5 mm [1]. The sensitivity of EUS for nodal staging, however, is far from perfect reaching about 62% in a recent meta-analysis including 20 studies [46], though superior to that of CT [47, 49].This may be due to that malignant lymphnodes in the abdomen tend to vary in morphology [53] even in patients without cancer [54], possibly because of co-existing inflammatory conditions. Thus, EUS-FNA has the potential to increase sensitivity. EUS-FNA has a sensitivity of 96.7% (95% CI, 82.2–99.9%) and a specificity of 100% (95% CI, 91.0–100%) for the diagnosis of para-aortic lymph node metastasis (compared to 53.3% and 97.5%, respectively for PET/CT) [55].

51.7.2 Stage 4 Disease

Distant metastatic disease is understandably better detected with CT and MRI than EUS [1]. However, EUS may occasionally detect small liver metastases undetected by other imaging modalities, small amount of ascites, and distant mediastinal lymph nodes [56, 57]. EUS-FNA has a sensitivity of 82–94% for the diagnosis of malignant disease in ascites or liver lesions [1], and in this case unnecessary surgery may be prevented.

To conclude, there is no evidence-based consensus on the optimal preoperative imaging assessment. Although EUS is superior to CT or MRI for T and N staging as well as vascular invasion of the spleno-portal confluence, CT or MRI may detect distant metastases and provide images that may be re-reviewed and discussed in multidisciplinary team meetings (MDTs). In practice, EUS is used as a supplement to high-quality CT for assessing resectability of PC [58]. If a pancreatic tumor

appears resectable on CT, most MDTs would not require further evaluation by means of EUS, as also supported by a recent Cochrane meta-analysis [59]. However, under certain circumstances such as the availability of a skilled endosonographer or in cases of doubtful invasion, EUS may be used along with CT aiming to provide complementary information. Regarding staging of pancreatic cancer, EUS accuracy appears to improve after 100 staging cases, and almost 80% of misstaging occurs early in the learning curve [60].However, the reported interobserver variablility does not only depend on the examiner's learning curve since inconsistencies in staging findings have been described even among experienced examiners given the *subjective* nature of the *examination.*

51.8 EUS-Guided Therapy

Pancreatic adenocarcinoma carries an extremely poor prognosis and 80–90% of patients have inoperable disease at diagnosis [61]. Development of resistance to chemotherapy and radiotherapy (attributed, in part, to PC hypovascularization and intense tissue desmoplasia) constitutes a barrier to the delivery of therapeutic agents and significantly limits therapeutic options [62].

Recently EUS applications, apart from diagnosis and staging of SPLs, have been extended to therapeutic purposes. The target population for such interventions includes patients with either locally advanced (for local treatment) and borderline resectable tumors (for downstaging) or those who refuse or are unfit for surgery. Due to the possibility of real-time observation of pancreatic lesions and to that of access to tumors in a minimally invasive fashion, interventional EUS may provide tumor targeted therapies(Table 51.6).

51.8.1 EUS-Fine Needle Injection (EUS-FNI) of Anti-tumor Agents

Antitumor agents can be directly delivered into tumor tissue by EUS-FNI, thus reducing systemic exposure and toxicity. First reports were published about 20 years ago [63] and since then various agents have been tested for this purpose. Apart from local injection of conventional chemotherapy agents (gemcitabine, paclitaxel) [64, 65], allogenic mixed lymphocyte cultures (cytoimplant), immature dendritic cells, as well as tumor necrosis factor-erade (TNFerade: replication deficient adenovector based gene therapy, allowing inducible translation of the human TNF-α gene) and gene-deleted replication selective viruses (HF10, BC819, ONYX-015) have been used [66, 67]. Their administration induces activation of the immune mechanism (cytokine or toxin secretion, viral replication and tumor cell apoptosis and death) ultimately causing tumor regression. Most of these agents

Table 51.6 EUS-guided treatment options for pancreatic cancer

Tumor targeted therapies	
(a) EUS-fine needle injection (EUS-FNI) of anti-tumor agents	• Cytoimplant(allogeneic mixed lymphocyte culture) • Tumor necrosis factor (TNF)-erade • Oncolytic viruses (HF10, BC819, ONYX-015) • Deliver chemotherapy directly in the pancreas [Gemcitabine, OncoGel(ReGel/paclitaxel)] • Immunotherapy: dendritic cells (DCs)
(b) EUS assisted radiotherapy	• Brachytherapy • EUS-guided interstitial chemoradiation • Stereotactic body radiotherapy (SBRt) after fiducial placement • Intensity-modulated radiotherapy (IMRT) after fiducial placement
(c) EUS-guided ablative techniques	• Radiofrequency ablation (RFA) • Cryothermal ablation • Photodynamic therapy (PDT) • EUS-guided ethanol ablation • Neodymium-doped yttrium aluminum garnet (Nd: YAG) laser probe • High-intensity focused ultrasound • Irreversible electroporation (IRE)

have shown a good safety profile [68] but are still under investigation as significant survival benefit has not been reached yet.

51.8.2 EUS-Assisted Radiotherapy

Conventional external beam radiation therapy is an option for controlling locally advanced PC. In order to minimize surrounding normal tissue damage and to provide precise and sufficient localization of the radiation alternative methods have been utilized. These mainly consist of interstitial brachytherapy and image-guided radiotherapy. Brachytherapy works by implanting radioactive seeds, that generate gamma rays leading to tumor tissue damage [69]. Iodine-125 is preferred to iridium-192 and palladium-103 mainly due to extended half-life and better efficacy for rapidly growing tumors such as PC [66]. EUS-guided brachytherapy tends to replace traditional seed implantation during open laparotomy or by CT guidance. According to two pilot studies, after EUS-guided brachytherapy partial tumor response ranged from 13.6% to 27% while stable disease was observed in 45.5–53% of cases [70, 71]. Transient pain reduction was reported by one out of three patients whereas adverse events ranged from 0% to 20% (pancreatitis, pseudocysts). No survival benefit was observed [71]. Placement of radioactive fiducial markers (mostly gold) inside or near the tumor prior to stereotactic body radiotherapy also allows precise tumor targeting. Pooled rates for fiducial migration and adverse events are 3% (95%

CI, 1.0–8.0) and 4% (95% CI, 3–7) respectively [72], whereas technical and clinical success was reached in about 90–98% of cases [72, 73].

51.8.3 EUS-Guided Ablative Techniques

Although not well-established as a therapeutic method, EUS-guided ablation of SPLs has shown promising results with reported resolution rates ranging from 62% to 100% [74]. The technique is based on the application of different types of energy (electrical/thermal), with the purpose to cause intralesional tissue damage and cellular necrosis. The most common reported ablative therapy for the treatment of SPLs is radiofrequency ablation (RFA) which apart from PC has also been proven to be efficient for treating functional pancreatic neuroendocrine tumors [75]. It consists of a needle inserted through the channel of the echoendoscope with a monopolar electrode on the distal part. In theory, RFA may lead to serious adverse events such as thermally induced pancreatitis and injuries to nearby structures and vessels. In a meta-analysis including 28 patients, only mild abdominal pain and mild pancreatitis were reported (25–33% and 14% respectively), while the technical success rate reached 100% [76]. Alternative EUS guided ablation techniques for SPLs include cryothermal ablation, photodynamic therapy (PDT), and EUS-guided ethanol ablation.

Although these techniques have generally shown high technical success and satisfactory safety profiles, they have failed to establish a statistically significant survival benefit [76]. Most of them are performed in referral centers by experienced endosonographers, most commonly in investigational settings. Well-designed randomized controlled trials are warranted to further estimate the safety, long term efficacy, and benefits of these techniques before they may become routine practice.

51.9 Conclusion

EUS is an indispensable method for detection, characterization, and differential diagnosis of solid pancreatic lesions. Image enhancement techniques used in combination with EUS, may aid in optimal lesion characterization, while EUS-guided sampling may help establish a cytopathology diagnosis with high accuracy and low risk for complications. Accurate local information with regards to staging and resectability can be also provided by EUS, supplementary to CT in inconclusive cases. Furthermore, minimally-invasive local techniques have been developed, and are still under investigation aiming to provide both active and palliative management within the treatment options of inoperable pancreatic cancer. It is likely that in the near future EUS will become increasingly important playing an integral role in the management of certain patients with SPLs.

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References

1. Kitano M, Yoshida T, Itonaga M, Tamura T, Hatamaru K, Yamashita Y. Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer. J Gastroenterol. 2019;54(1):19–32.
2. Faigel D, Eisen G, Baron T, Dominitz J, Goldstein J, Hirota W, et al. Preparation of patients for GI endoscopy. Gastrointest Endosc. 2003;57:446–50.
3. Palazzo L. How to perform EUS in the pancreaticobiliary area. Minerva Med. 2014;105(5):371–89.
4. Early DS, Lightdale JR, Vargo JJ 2nd, Acosta RD, Chandrasekhara V, Chathadi KV, et al. Guidelines for sedation and anesthesia in GI endoscopy. Gastrointest Endosc. 2018;87(2):327–37.
5. Kersting S, Janot MS, Munding J, Suelberg D, Tannapfel A, Chromik AM, et al. Rare solid tumors of the pancreas as differential diagnosis of pancreatic adenocarcinoma. JOP. 2012;13(3):268–77.
6. Kim SS, Choi GC, Jou SS. Pancreas ductal adenocarcinoma and its mimics: review of cross-sectional imaging findings for differential diagnosis. J Belg Soc Radiol. 2018;102(1):71.
7. Dietrich CF, Sahai AV, D'Onofrio M, Will U, Arcidiacono PG, Petrone MC, et al. Differential diagnosis of small solid pancreatic lesions. Gastrointest Endosc. 2016;84(6):933–40.
8. Low G, Panu A, Millo N, Leen E. Multimodality imaging of neoplastic and nonneoplastic solid lesions of the pancreas. Radiographics. 2011;31(4):993–1015.
9. Okun SD, Lewin DN. Non-neoplastic pancreatic lesions that may mimic malignancy. Semin Diagn Pathol. 2016;33(1):31–42.
10. Borbath I, Van Beers BE, Lonneux M, Schoonbroodt D, Geubel A, Gigot JF, et al. Preoperative assessment of pancreatic tumors using magnetic resonance imaging, endoscopic ultrasonography, positron emission tomography and laparoscopy. Pancreatology. 2005;5(6):553–61.
11. De Angelis C, Brizzi RF, Pellicano R. Endoscopic ultrasonography for pancreatic cancer: current and future perspectives. J Gastrointest Oncol. 2013;4(2):220–30.
12. Yamaguchi K, Okusaka T, Shimizu K, Furuse J, Ito Y, Hanada K, et al. Clinical practice guidelines for pancreatic cancer 2016 from the Japan Pancreas Society: a synopsis. Pancreas. 2017;46(5):595–604.
13. Horwhat JD, Paulson EK, McGrath K, Stanley Branch M, Baillie J, Tyler D, et al. A randomized comparison of EUS-guided FNA versus CT or US-guided FNA for the evaluation of pancreatic mass lesions. Gastrointest Endosc. 2006;63(7):966–75.
14. Volmar KE, Vollmer RT, Jowell PS, Nelson RC, Xie HB. Pancreatic FNA in 1000 cases: a comparison of imaging modalities. Gastrointest Endosc. 2005;61(7):854–61.
15. Dumonceau JM, Deprez PH, Jenssen C, Iglesias-Garcia J, Larghi A, Vanbiervliet G, et al. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline – updated January 2017. Endoscopy. 2017;49(7):695–714.
16. Chen VK, Arguedas MR, Kilgore ML, Eloubeidi MA. A cost-minimization analysis of alternative strategies in diagnosing pancreatic cancer. Am J Gastroenterol. 2004;99(11):2223–34.
17. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass? A meta-analysis and systematic review. Pancreas. 2013;42(1):20–6.
18. Jani BS, Rzouq F, Saligram S, Lim D, Rastogi A, Bonino J, et al. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic lesions: a systematic review of technical and procedural variables. N Am J Med Sci. 2016;8(1):1–11.
19. Polkowski M, Jenssen C, Kaye P, Carrara S, Deprez P, Gines A, et al. Technical aspects of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) technical guideline – March 2017. Endoscopy. 2017;49(10):989–1006.

20. Facciorusso A, Wani S, Triantafyllou K, Tziatzios G, Cannizzaro R, Muscatiello N, et al. Comparative accuracy of needle sizes and designs for EUS tissue sampling of solid pancreatic masses: a network meta-analysis. Gastrointest Endosc. 2019;90(6):893–903.e7.
21. Lee JK, Choi JH, Lee KH, Kim KM, Shin JU, Lee JK, et al. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. Gastrointest Endosc. 2013;77(5):745–51.
22. Bang JY, Magee SH, Ramesh J, Trevino JM, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy. 2013;45(6):445–50.
23. Schmidt RL, Witt BL, Matynia AP, Barraza G, Layfield LJ, Adler DG. Rapid on-site evaluation increases endoscopic ultrasound-guided fine-needle aspiration adequacy for pancreatic lesions. Dig Dis Sci. 2013;58(3):872–82.
24. Wani S, Mullady D, Early DS, Rastogi A, Collins B, Wang JF, et al. The clinical impact of immediate on-site cytopathology evaluation during endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: a prospective multicenter randomized controlled trial. Am J Gastroenterol. 2015;110(10):1429–39.
25. Collins BT, Murad FM, Wang JF, Bernadt CT. Rapid on-site evaluation for endoscopic ultrasound-guided fine-needle biopsy of the pancreas decreases the incidence of repeat biopsy procedures. Cancer Cytopathol. 2013;121(9):518–24.
26. Conti CB, Cereatti F, Grassia R. Endoscopic ultrasound-guided sampling of solid pancreatic masses: the fine needle aspiration or fine needle biopsy dilemma. Is the best needle yet to come? World J Gastrointest Endosc. 2019;11(8):454–71.
27. Khan MA, Grimm IS, Ali B, Nollan R, Tombazzi C, Ismail MK, et al. A meta-analysis of endoscopic ultrasound-fine-needle aspiration compared to endoscopic ultrasound-fine-needle biopsy: diagnostic yield and the value of onsite cytopathological assessment. Endosc Int Open. 2017;5(5):E363–e75.
28. Saftoiu A, Vilmann P, Guldhammer Skov B, Georgescu CV. Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: a prospective study. Scand J Gastroenterol. 2007;42(1):117–25.
29. Yarandi SS, Runge T, Wang L, Liu Z, Jiang Y, Chawla S, et al. Increased Incidence of benign pancreatic pathology following pancreaticoduodenectomy for presumed malignancy over 10 years despite increased use of endoscopic ultrasound. Diagn Ther Endosc. 2014;2014:701535.
30. Ardengh JC, Lopes CV, de Lima LF, Venco F, Santo GC, Begnami MD, et al. Cell block technique and cytological smears for the differential diagnosis of pancreatic neoplasms after endosonography-guided fine-needle aspiration. Acta Gastroenterol Latinoam. 2008;38(4):246–51.
31. Kim J-H, Lee SJ, Moon S-H, Kim HJ, Kim HJ, Song IH, et al. Incremental value of cell block preparations over conventional smears alone in the evaluation of EUS-FNA for pancreatic masses. Hepato-Gastroenterology. 2014;61(135):2117–22.
32. Early DS, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Evans JA, et al. Adverse events associated with EUS and EUS with FNA. Gastrointest Endosc. 2013;77(6):839–43.
33. Lee KH, Kim EY. Risk factors associated with adverse events during endoscopic ultrasound-guided tissue sampling. PLoS One. 2017;12(12):e0189347.
34. Minaga K, Takenaka M, Katanuma A, Kitano M, Yamashita Y, Kamata K, et al. Needle tract seeding: an overlooked rare complication of endoscopic ultrasound-guided fine-needle aspiration. Oncology. 2017;93(Suppl 1):107–12.
35. Matsui T, Nishikawa K, Yukimoto H, Katsuta K, Nakamura Y, Tanaka S, et al. Needle tract seeding following endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer: a report of two cases. World J Surg Oncol. 2019;17(1):134.
36. Ngamruengphong S, Xu C, Woodward TA, Raimondo M, Stauffer JA, Asbun HJ, et al. Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. Endoscopy. 2013;45(8):619–26.

37. Kim SH, Woo YS, Lee KH, Lee JK, Lee KT, Park JK, et al. Preoperative EUS-guided FNA: effects on peritoneal recurrence and survival in patients with pancreatic cancer. Gastrointest Endosc. 2018;88(6):926–34.
38. Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003;58(5):690–5.
39. Chantarojanasiri T, Kongkam P. Endoscopic ultrasound elastography for solid pancreatic lesions. World J Gastrointest Endosc. 2017;9(10):506–13.
40. Altonbary AY, Hakim H, El-Shamy AM. Diagnostic efficacy of endoscopic ultrasound elastography in differentiating solid pancreatic lesions: a single-center experience. Clin Endosc. 2019;52(4):360–4.
41. Saftoiu A, Vilmann P, Bhutani MS. The role of contrast-enhanced endoscopic ultrasound in pancreatic adenocarcinoma. Endosc Ultrasound. 2016;5(6):368–72.
42. Mei S, Wang M, Sun L. Contrast-enhanced EUS for differential diagnosis of pancreatic masses: a meta-analysis. Gastroenterol Res Pract. 2019;2019:9.
43. Iordache S, Costache MI, Popescu CF, Streba CT, Cazacu S, Saftoiu A. Clinical impact of EUS elastography followed by contrast-enhanced EUS in patients with focal pancreatic masses and negative EUS-guided FNA. Med Ultrason. 2016;18(1):18–24.
44. Machicado J, Rebours V, Yadav D. Epidemiology of chronic pancreatitis. 2016. doi:https://doi.org/10.3998/panc.2016.13.
45. Narkhede RA, Desai GS, Prasad PP, Wagle PK. Diagnosis and management of pancreatic adenocarcinoma in the background of chronic pancreatitis: core issues. Dig Dis. 2019;37(4):315–24.
46. Li JH, He R, Li YM, Cao G, Ma QY, Yang WB. Endoscopic ultrasonography for tumor node staging and vascular invasion in pancreatic cancer: a meta-analysis. Dig Surg. 2014;31(4–5):297–305.
47. DeWitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol. 2006;4(6):717–25.
48. Snady H. EUS criteria for vascular invasion: analyzing the meta-analysis. Gastrointest Endosc. 2007;65(6):798–807.
49. Nawaz H, Fan CY, Kloke J, Khalid A, McGrath K, Landsittel D, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP. 2013;14(5):484–97.
50. Yang R, Lu M, Qian X, Chen J, Li L, Wang J, et al. Diagnostic accuracy of EUS and CT of vascular invasion in pancreatic cancer: a systematic review. J Cancer Res Clin Oncol. 2014;140(12):2077–86.
51. Imazu H, Uchiyama Y, Matsunaga K, Ikeda K, Kakutani H, Sasaki Y, et al. Contrast-enhanced harmonic EUS with novel ultrasonographic contrast (sonazoid) in the preoperative T-staging for pancreaticobiliary malignancies. Scand J Gastroenterol. 2010;45(6):732–8.
52. Iglesias Garcia J, Larino Noia J, Dominguez Munoz JE. Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer. Rev Esp Enferm Dig. 2009;101(9):631–8.
53. Hoshikawa M, Ogata S, Nishikawa M, Kimura A, Einama T, Noro T, et al. Pathomorphological features of metastatic lymph nodes as predictors of postoperative prognosis in pancreatic cancer. Medicine. 2019;98(5):e14369.
54. Kalaitzakis E, Sadik R, Doig L, Meenan J. Defining the lymph node burden in a Northern European population without malignancy: the potential effect of geography in determining a need for FNA? Dis Esophagus. 2009;22(5):409–17.
55. Kurita A, Kodama Y, Nakamoto Y, Isoda H, Minamiguchi S, Yoshimura K, et al. Impact of EUS-FNA for preoperative para-aortic lymph node staging in patients with pancreatobiliary cancer. Gastrointest Endosc. 2016;84(3):467–75.e1.
56. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. Gastrointest Endosc. 1999;50(3):357–61.

57. Nguyen PT, Chang KJ. EUS in the detection of ascites and EUS-guided paracentesis. Gastrointest Endosc. 2001;54(3):336–9.
58. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
59. Tamburrino D, Riviere D, Yaghoobi M, Davidson BR, Gurusamy KS. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016;9:Cd011515.
60. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999;50(6):786–91.
61. Weinberg BA, Yabar CS, Brody JR, Pishvaian MJ. Current standards and novel treatment options for metastatic pancreatic adenocarcinoma. Oncology (Williston Park). 2015;29(11):809–20.
62. Ware MJ, Curtis LT, Wu M, Ho JC, Corr SJ, Curley SA, et al. Pancreatic adenocarcinoma response to chemotherapy enhanced with non-invasive radio frequency evaluated via an integrated experimental/computational approach. Sci Rep. 2017;7(1):3437.
63. Chang KJ, Nguyen PT, Thompson JA, Kurosaki TT, Casey LR, Leung EC, et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000;88(6):1325–35.
64. Levy MJ, Alberts SR, Bamlet WR, Burch PA, Farnell MB, Gleeson FC, et al. EUS-guided fine-needle injection of gemcitabine for locally advanced and metastatic pancreatic cancer. Gastrointest Endosc. 2017;86(1):161–9.
65. Matthes K, Mino-Kenudson M, Sahani DV, Holalkere N, Fowers KD, Rathi R, et al. EUS-guided injection of paclitaxel (OncoGel) provides therapeutic drug concentrations in the porcine pancreas (with video). Gastrointest Endosc. 2007;65(3):448–53.
66. Han J, Chang KJ. Endoscopic ultrasound-guided direct intervention for solid pancreatic tumors. Clin Endosc. 2017;50(2):126–37.
67. Moutinho-Ribeiro P, Liberal R, Macedo G. Endoscopic ultrasound in pancreatic cancer treatment: facts and hopes. Clin Res Hepatol Gastroenterol. 2019;43(5):513–21.
68. Han J, Chang KJ. Endoscopic ultrasound-guided direct intervention for solid pancreatic tumors. Clin Endosc. 2017;50(2):126–37.
69. Suzuki R, Irisawa A, Bhutani MS. Endoscopic ultrasound-guided oncologic therapy for pancreatic cancer. Diagn Ther Endosc. 2013;2013:157581.
70. Sun S, Xu H, Xin J, Liu J, Guo Q, Li S. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy. 2006;38(4):399–403.
71. Jin Z, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy. 2008;40(4):314–20.
72. Coronel E, Cazacu IM, Sakuraba A, Luzuriaga Chavez AA, Uberoi A, Geng Y, et al. EUS-guided fiducial placement for GI malignancies: a systematic review and meta-analysis. Gastrointest Endosc. 2019;89(4):659–70.e18.
73. Fabbri C, Luigiano C, Lisotti A, Cennamo V, Virgilio C, Caletti G, et al. Endoscopic ultrasound-guided treatments: are we getting evidence based—a systematic review. World J Gastroenterol. 2014;20(26):8424–48.
74. Paik WH, Lee SH, Jang S. Future perspectives on endoscopic ultrasonography-guided therapy for pancreatic neoplasm. Clin Endosc. 2018;51(3):229–34.
75. McCarty TR, Rustagi T. New indications for endoscopic radiofrequency ablation. Clin Gastroenterol Hepatol. 2018;16(7):1007–17.
76. Changela K, Patil R. Endoscopic ultrasound-guided radiofrequency ablation of the pancreatic tumors: a promising tool in management of pancreatic tumors. Can J Gastroenterol Hepatol. 2016;2016:4189358.

Chapter 52
The Role of Laparoscopic Staging in Pancreatic Cancer

Helen S. Earley, Vikram Tewatia, and Kevin C. Conlon

Take Home Messages

- Use of laparoscopic staging may be of benefit to avoid a non- therapeutic laparotomy in a select cohort of patients undergoing surgery for pancreatic cancer.
- Laparoscopic US enhances the ability to determine resectability of these tumours.
- In most studies reported, CT and laparoscopy reduces the rate of unresectability at laparotomy.
- It has been shown to be cost effective.

Pearls and Pitfalls

- Use of an angled telescope facilitates the examination of the celiac axis and biopsy of lymphadenopathy.
- Maintaining haemostasis at all times is essential, as bleeding will obscure vision and impact on the operating surgeon's ability to assess the tumour, particularly when performing biopsy of celiac or hepatic lymph nodes
- Peritoneal washings for cytology should be obtained *prior* to any manipulation of the tumour.

Future Perspectives

- More recent studies (post 2000) evaluating the effectiveness of staging laparoscopy after employing more modern pre-operative imaging.

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52.1 Introduction

One of the major diagnostic challenges associated with pancreatic cancer is its' indolent course. Currently no means of early detection exists, resulting in most patients presenting at an advanced stage. At present only 15–20% of patients with the disease have a tumour that is amenable to curative resection [1, 2]. The average survival time of patients post resection is estimated at between 12 and 24 months [3, 4]. For those whose condition is inoperable the average survival time is even less [5]. Whether a tumour is amenable to surgery is therefore an important prognostic indicator. Staging of pancreatic cancer aims to classify tumours as localized, locally advanced or metastastatic and the staging will have implications for further management options.

Accurate initial staging is paramount to determine whether a tumour is amenable to operative treatment, while also aiming to minimize unnecessary intervention [1]. Tumours may also be referred to as resectable (localized), borderline resectable (BLR) (local invasion) or unresectable [6]. Even in those whose initial staging investigations indicate resectability, a number of factors have been linked to an increased risk of unresectability at the time of exploratory laparotomy. Indeed despite the improvement of radiologic staging investigations in recent years, current literature suggests that up to 30% of patients undergo a non-therapeutic laparotomy in the setting of advanced pancreatic cancer [3, 7]. In such cases laparoscopic staging (LS) may play a role.

The aim of this chapter is to discuss the current evidence and controversies around LS in pancreatic cancer.

52.2 Staging in Pancreatic Cancer

The aim of LS in pancreatic cancer is to detect or outrule local or regional disease spread prior to further operative management. It has been shown to be a safe and cost-effective way of directing appropriate therapy and avoiding unnecessary intervention when used in conjunction with appropriate imaging modalities [8].

Laparoscopy allows direct visualisation of the peritoneal cavity and can detect peritoneal spread of the cancer or the involvement of other abdominal organs that may not be apparent on imaging. Involvement of the liver is demonstrated in Fig. 52.1. Laparoscopic staging was popularised by Cuscheri in the late 1970s and early 1980s, who found that peritoneal metastasis and omental deposits were only detected at laparoscopy, rendering five out of nine patients unresectable and proposed that LS should be considered in all patients in whom a subsequent laparotomy was being considered [9, 10]. Of note, it can also detect small subcapsular hepatic metastasis of <10 mm in diameter.

Some of the reported advantages of LS include reduced operative morbidity, postoperative pain and operating costs associated with non-therapeutic laparotomy.

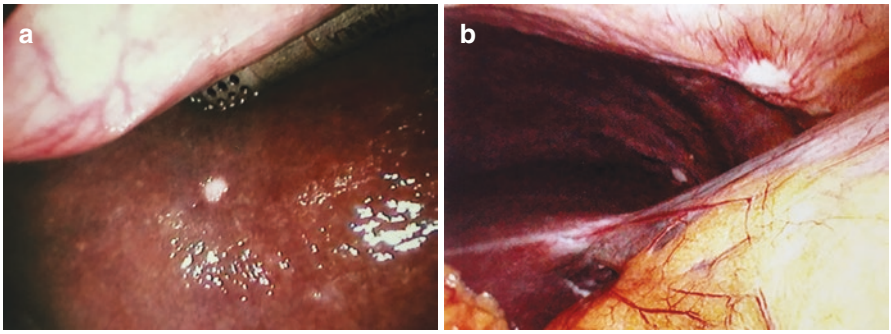

Fig. 52.1 (**a**) Peritoneal metastases identified at laparoscopy. (**b**) Liver surface evaluation performed during laparoscopy showing suspicious lesions

It has also been reported to be associated with a higher likelihood of receiving systemic therapy in patients with unresectable pancreatic cancer compared to exploratory laparotomy and surgical palliation [3].

However, a number of criticisms of laparoscopy in this setting arose, including that it allowed only two-dimensional inspection of the liver and the peritoneal cavity, as well as a lack of tactile sensation which limited the identification of intraparenchymal hepatic metastases and evaluation of retroperitoneal tumour-vessel relationships, both of which were of key importance in further operative planning. In an attempt to address these perceived shortcomings of the procedure, John et al., developed the concept of laparoscopic ultrasound (LUS) in 1995 [11]. The development of LUS improved diagnostic yield by allowing the surgeon to examine the liver parenchyma and proximity of the tumour to major vessels such as the SMA and porta hepatis. Studies reported sensitivities of greater than 90% for predicting operability in pancreatic tumours [8, 12–15]. In 1996 Conlon et al., described a multiport technique to stage and assess resectability of peripancreatic malignancy, mimicking the surgical assessment performed at open operation [16]. In addition to assessment of liver and peritoneal cavity, this technique involved extended laparoscopy to evaluate the lesser sac, porta hepatis, duodenum, transverse mesocolon and celiac and portal vessels. It was associated with a 100% positive predictive value, obviating the need for open exploration in patients with potentially resectable peripancreatic tumours.

In addition to direct visualization, at the time of laparoscopy biopsy or washings for cytology can be performed if a suspicious liver, omental or peritoneal lesion is seen. Patients undergoing LS are most often deemed to have unresectable disease as a result of occult liver metastases and peritoneal tumour seeding [17, 18]. Positive lavage cytology is associated with lower resectability and lower survival rates [19]. In the majority of centres cytology is not available at the time of staging laparoscopy.

Borderline resectable (BLR) tumours are a subgroup of pancreatic ductal cancers in which LS may play a role in. BLR tumours comprise an imprecise entity that lie

between resectable and unresectable disease on the initial clinical evaluation. This is usually due to vessel involvement that renders an R0 resection unlikely to be achieved [20, 21]. A consensus on the definition of BLR pancreatic cancer has not yet been reached. The most commonly accepted definition (adopted by American Hepatopancreaticobiliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/National Comprehensive Cancer Network (NCCN)), is:

> The presence of venous involvement of the superior mesenteric vein (SMV)/portal vein (PV) demonstrating tumour abutment, encasement, or short segment venous occlusion, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction; gastroduodenal artery encasement up to the hepatic artery (HA) and short segment encasement/direct tumour abutment of the HA with no extension to the coeliac axis; or tumour-superior mesenteric artery (SMA) involvement <180° [22]. BLR tumours may benefit from resection after neoadjuvant therapy and re-staging [21–24]. Some centres recommend LS in certain patients with BLR pancreatic cancer prior to initiation of neoadjuvant therapy in order to improve the reliability of initial staging [21, 23, 25]. The third St. Gallen EORTC Gastrointestinal Conference in 2016 found that 38% of those on the panel would perform LS in this patient cohort [6] (Box 52.1).

Box 52.1 Definition: Borderline Resectable Pancreatic Cancer

- The presence of venous involvement of the SMV/PV demonstrating tumour abutment, encasement, or short segment venous occlusion, but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the HA and short segment encasement/direct tumour abutment of the HA with no extension to the coeliac axis.
- Tumour-SMA involvement <180°.

52.3 Controversies in Laparoscopic Staging

Despite its apparent benefits, LS is not universally employed by pancreatic surgeons. Opinions range from recommending its routine use before laparotomy, to not performing LS in any setting [22]. Most recently, data from the National Surgical Quality Improvement Program for patients with pancreatic cancer published in 2019 showed that SL was becoming less common and just 10% of patients who underwent exploratory laparotomy without further resection or bypass had a staging laparoscopy [26].

An argument against routine LS has arisen in recent years, as the proportion of patients found to have metastatic disease at laparoscopy is decreasing due to the increased sensitivity of imaging, and in particular Computerised Tomography (CT) [3]. Critics argue that if imaging is appropriately employed, a minority of patients would benefit from the addition of LS. CT technology has evolved rapidly in the past 20 years, with the availability of spiral CT, multichannel CT with IV contrast and multi detector—row CT and multiphase helical CT, all of which produce varying results in terms of sensitivity and specificity. The standard imaging protocol recommended by NCCN guidelines at present is triphasic pancreatic CT. Current CT scanners are thought to have a sensitivity of up to 90% for detection and a specificity of up to 80–90% for staging in pancreatic ductal cancer [27]. However some limitations remain, including limited sensitivity of CT in detecting small metastasis and the ability to distinguish between reactive and malignant lymphadenopathy [12]. Despite the improvement of current staging investigations, a high proportion of patients still undergo a non-therapeutic laparotomy for pancreatic cancer [7, 26]. These data would suggest that LS still has a role to play, the challenge being in determining which patients are most likely to benefit [1, 3, 7, 26, 28].

A 10 year review of pancreatic cancer and peri-pancreatic neoplasms at Memorial Sloan Kettering conducted by White et al. between 1995 and 2005 found that the yield of SL decreased during the study period. However, it did note that of the 1045 patients deemed resectable on imaging, 145 (14%) had radiologically occult metastasis at subsequent laparoscopy [17]. Interestingly, the yield varied depending on whether pre-operative imaging was performed within the institution or externally. With internal imaging a yield of 8.4% was found, whereas after external imaging this rose to 17% ($p < 0.01$), indicating that variation in imaging modality or interpretation of CTs by different radiologist may influence the value of staging CT. This study also noted that for the subgroup of patients with pancreatic tumours ($n = 838$) patients with adenocarcinoma had a substantially higher risk of radiologically occult unresectable disease compared to patients with other histologies.

In 2016 a Cochrane Review was conducted to assess the diagnostic accuracy of LS after CT for assessing resectability with curative intent in pancreatic and periampullary cancer. Sixteen studies with a total of 1146 patients were included for review. The summary sensitivity of diagnostic laparoscopy was 64.4% (95% confidence interval (CI) 50.1–76.6%). Assuming a pre-test probability of 41.4%, the post-test probability of unresectable disease for participants with a negative test result was 0.20 (95% CI 0.15–0.27). This indicates that if a person is said to have resectable disease after diagnostic laparoscopy and CT scan, there is a 20% probability that their cancer will be unresectable compared to a 41% probability for those receiving CT alone. A subgroup analysis of people with pancreatic cancer gave a summary sensitivity of 67.9% (95% CI 41.1–86.5%). The post-test probability of unresectable disease after being considered resectable on both CT and diagnostic laparoscopy was 18% compared to 40.0% for those receiving CT alone. The authors concluded that on average, using diagnostic laparoscopy with biopsy confirmation of suspicious lesions prior to laparotomy would avoid 21 unnecessary laparotomies in 100 people in whom resection of cancer with curative intent is planned.

These results were replicated in a meta-analysis of 12 studies conducted by Ta et al., published in 2019, who found that between 14% and 38% of patients had radiologically occult metastases that rendered them unresectable, with an overall rate of 20% unresectability reported for the 2486 patients included in analysis [18]. Of those who underwent laparotomy after LS, a further 5% were deemed unresectable. Liver metastasis was the most common reason for non-resectability in (49.6%), followed by sites not specified (18.5%) and peritoneal metastases (17.4%). After laparotomy, vascular involvement was the most common reason for non-resectability (40.6%). None of the included studies reported the rate of additional disease after LS in patients reported as specifically borderline resectable after CT [18].

In terms of sensitivity and specificity of CT in the studies included, the ranges were as follows; sensitivity (0.26–0.83), specificity (1.00–1.00), positive predictive value (100–100%), negative predictive value (62–86%) were reported. However, the authors noted that a limitation of the currently available evidence on this subject was that the majority of studies published to date were performed before 2000, before the introduction of more advanced pancreatic imaging protocols including high resolution CT, MRI or PET CT were developed. This highlighted a need for newer studies evaluating the effectiveness of staging laparoscopy after employing more modern pre-operative imaging as well as the interpretation of imaging by specialist radiologists in a multi-disciplinary or tumour board assessment.

A number of studies have aimed to address the question of whether LS represents a cost effective measure in pancreatic cancer. A large cost analysis study in the United States (US) found that routine SL was favoured, with an increased cost effectiveness ratio of $10,695 US dollars per quality adjusted life month in patients undergoing primary surgery as their mainstay of treatment [29]. A further study by Morris et al. found LS to be cost effective for potentially resectable pancreatic cancer, but not for ampullary cancer [30].

52.4 Indications for Laparoscopic Staging

Based on the above discussion, pre-operative imaging alone may not provide sufficient accuracy to proceed to successful therapeutic surgical resection in all cases. The aforementioned meta-analysis on the role of LS in resectable and BLR pancreatic cancer concluded that LS is worth consideration in cases where pre-operative imaging demonstrates resectable or radiographically indeterminate disease [18]. More specifically, an algorithm for LS in pancreatic surgery has previously been published by Memba et al. in 2018, who suggested that patients with tumours meeting the following criteria should be considered for laparoscopic staging [31]:

- Tumours larger than 3 cm and markedly elevated CA 19-9.
- Indeterminate metastatic disease on imaging (equivocal peritoneal/liver metastases, low-volume ascites).
- In preoperative staging of BLR pancreatic cancer, in order to select more accurately the patients for neoadjuvant protocols.

These recommendations were similar to those published in 2016 by De Rosa et al. [3]. Although some studies on this topic also suggested a role for tumour location (body and tail of the pancreas), CEA levels, weight loss or jaundice, the authors felt there was insufficient evidence to support their inclusion into the above algorithm [3, 12, 22, 25]. The National Cancer Comprehensive Network (NCCN) have recently published guidelines [32], which recommend staging laparoscopy in patients who meet any of the following criteria:

- CA 19-9 level >150 U/mL
- Low-volume ascites
- Tumor in the body of the pancreas
- Borderline resectable tumor
- Tumor size >3 cm
- Common bile duct lymphadenopathy

52.5 Surgical Technique of Laparoscopic Staging

LS can either be performed immediately prior to laparotomy as part of a scheduled pancreatectomy or as a separate procedure. The advantage of performing it as part of the definitive surgical procedure is that the patient is subjected to one hospital admission and general anaesthetic. It is however, associated with a risk of wasted theatre resources, should the patient be diagnosed with unresectable disease and the planned pancreatectomy cancelled.

52.5.1 Positioning and Trocar Placement

LS is performed under general anesthetic with the patient in supine position. A periumbilical skin incision and open Hasson technique [33] is most frequently performed to gain access to the abdomen. A 10 mm blunt port is placed to introduce the laparoscope. Pneumoperitoneum is maintained between 8 and 12 mm Hg. Additional 5 mm trocars are used at the discretion of the surgeon for further exposure and for potential biopsies, ultrasound or intervention as indicated. The secondary ports are placed in the line of a planned skin incision for subsequent laparotomy.

52.5.2 Intrabdominal Examination

A 30° angled scope is employed to allow inspection of the intra-abdominal cavity, including liver, gallbladder, stomach, intestine, pelvic organs, and visible retroperitoneal surfaces (Fig. 52.1a, b). Intraperitoneal adhesions, if present, are

divided. If ascitic fluid is present, it may be aspirated for cytology. Peritoneal washings for cytology may also be collected after instilling between 200 and 400 cc of saline into both upper quadrants and pelvis *prior* to any manipulation of the tumour. After careful inspection of the peritoneal cavity, fine needle aspiration (FNA) or biopsies of any suspicious serosal lesions is performed. The tumour is then examined for extent, size and mobility to help determine resectability. Systematic inspection of the liver and diaphragmatic surface after positioning the patient in a 20° reverse Trendelenburg is carried out. Incision of the gastro-hepatic omentum, exposing the caudate lobe, coeliac axis and inferior vena cava are performed. HA is visualised and biopsies of portal, perigastric and celiac lymph nodes, if enlarged, are carried out. The lesser sac is entered with the camera via right upper quadrant port (10 or 5 mm, if a 5 mm camera is used) for evaluation of the tumour. The patient is positioned at 10° Trendelenburg and the greater omentum is moved to the left upper quadrant. The transverse colon is lifted to visualise the ligament of Treitz, transverse mesocolon, middle colic vein and to inspect for lymphadenopathy in the region.

52.5.3 Laparoscopic Ultrasonography

Laparoscopic ultrasound (LUS) is performed to assess for small intraparenchymal hepatic lesions, invasion of PV, SMA or SMV, as well as peripancreatic extension of the tumour and local and regional lymph nodes. A 6–10 MHz linear or curvilinear-array transducer is placed. In addition, Doppler allows vessel identification and assessment of tumor-vessel surface. LUS can also facilitate biopsies and needle aspirations of suspicious lesions.

Indicators that a tumour is not amenable to resection include: direct visualisation of hepatic, serosal, peritoneal or omental metastasis or histological confirmation of these by frozen section; peripancreatic tumour extension, celiac or portal positive lymph nodes; high PV involvement by tumour or invasion and/or encasement of the celiac trunk, HA or SMA [31, 34–37].

This operative approach described above utilises laparoscopic skills which should be easily performed by the majority of surgeons mimicking the assessment of resectability performed at open exploration. The use of an angled telescope facilitates the examination of the celiac axis and biopsy of any suspect lymphadenopathy. As with any advanced laparoscopic technique excellent optics and gentle tissue handling are required. Care must be taken to secure haemostasis at all times as bleeding will obscure vision and impact on the operating surgeon's ability to assess the tumour. This is particularly important when performing a biopsy of celiac or hepatic lymph nodes. Overall, our experience over the last thirty years has been that laparoscopic staging is safe and can be performed with minimal morbidity.

52.6 Conclusion

In summary, selective use of laparoscopic staging may be of benefit to avoid a non-therapeutic laparotomy in a select cohort of patients undergoing surgery for pancreatic cancer. The addition of LUS during laparoscopy enhances the ability to determine resectability of these tumours. Current guidelines suggest a high CA19-9, presence of ascites or bile duct lymphadenopathy, pancreatic body tumour, BLR tumour or tumour size >3 cm as factors influencing the decision to proceed with laparoscopic staging. In most studies, a combination of multiphase, thin-slice CT and laparoscopy reduces the rate of unresectability to 10–20% at laparotomy, compared to the 30–50% rate historically reported for exploration for pancreatic cancer (Box 52.2).

Box 52.2 NCCN Guidelines for Staging Laparoscopy in Pancreatic Cancer

- CA 19-9 level >150 U/mL
- Low-volume ascites
- Tumor in the body of the pancreas
- Borderline resectable tumor
- Tumor size >3 cm
- Common bile duct lymphadenopathy

References

1. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2013;11:CD009323.
2. Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford). 2008;10(1):58–62.
3. De Rosa A, Cameron IC, Gomez D. Indications for staging laparoscopy in pancreatic cancer. HPB. 2016;18(1):13–20.
4. Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, et al. Recent progress in pancreatic cancer. CA Cancer J Clin. 2013;63(5):318–48.
5. Shankar A, Russell RC. Recent advances in the surgical treatment of pancreatic cancer. World J Gastroenterol. 2001;7(5):622–6.
6. Lutz MP, Zalcberg JR, Ducreux M, Aust D, Bruno MJ, Buchler MW, et al. 3rd St. Gallen EORTC Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of pancreatic cancer. Eur J Cancer (Oxford, England: 1990). 2017;79:41–9.

7. van der Geest LGM, Lemmens V, de Hingh I, van Laarhoven C, Bollen TL, Nio CY, et al. Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. Br J Surg. 2017;104(11):1568–77.
8. Conlon KC, Minnard EA. The value of laparoscopic staging in upper gastrointestinal malignancy. Oncologist. 1997;2(1):10–7.
9. Cuschieri A. Laparoscopy for pancreatic cancer: does it benefit the patient? Eur J Surg Oncol. 1988;14(1):41–4.
10. Cuschieri A, Hall AW, Clark J. Value of laparoscopy in the diagnosis and management of pancreatic carcinoma. Gut. 1978;19(7):672–7.
11. John TG, Greig JD, Carter DC, Garden OJ. Carcinoma of the pancreatic head and periampullary region. Tumor staging with laparoscopy and laparoscopic ultrasonography. Ann Surg. 1995;221(2):156–64.
12. Camacho D, Reichenbach D, Duerr GD, Venema TL, Sweeney JF, Fisher WE. Value of laparoscopy in the staging of pancreatic cancer. JOP. 2005;6(6):552–61.
13. Hann LE, Conlon KC, Dougherty EC, Hilton S, Bach AM, Brennan MF. Laparoscopic sonography of peripancreatic tumors: preliminary experience. AJR Am J Roentgenol. 1997;169(5):1257–62.
14. de Werra C, Quarto G, Aloia S, Perrotta S, Del Giudice R, Di Filippo G, et al. The use of intraoperative ultrasound for diagnosis and stadiation in pancreatic head neoformations. Int J Surg. 2015;21(Suppl 1):S55–8.
15. Minnard EA, Conlon KC, Hoos A, Dougherty EC, Hann LE, Brennan MF. Laparoscopic ultrasound enhances standard laparoscopy in the staging of pancreatic cancer. Ann Surg. 1998;228(2):182–7.
16. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg. 1996;223(2):134–40.
17. White R, Winston C, Gonen M, D'Angelica M, Jarnagin W, Fong Y, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. J Am Coll Surg. 2008;206(3):445–50.
18. Ta R, O'Connor DB, Sulistijo A, Chung B, Conlon KC. The role of staging laparoscopy in resectable and borderline resectable pancreatic cancer: a systematic review and meta-analysis. Dig Surg. 2019;36(3):251–60.
19. Merchant NB, Conlon KC, Saigo P, Dougherty E, Brennan MF. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg. 1999;188(4):421–6.
20. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, et al. Predicting factors for unresectability in patients with pancreatic ductal adenocarcinoma. J Hepatobiliary Pancreat Sci. 2014;21(9):648–53.
21. Mahipal A, Frakes J, Hoffe S, Kim R. Management of borderline resectable pancreatic cancer. World J Gastrointest Oncol. 2015;7(10):241–9.
22. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
23. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006;13(8):1035–46.
24. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol. 2014;20(31):10740–51.
25. O'Connor DBT, Sulistijo A, Chung B, Conlon KC. The utility of staging laparoscopy for potentially resectable pancreatic cancer: a systematic review. Pancreatology. 2016;16(3):S104.
26. Paracha M, Van Orden K, Patts G, Tseng J, McAneny D, Sachs T. Opportunity lost? Diagnostic laparoscopy in patients with pancreatic cancer in the national surgical quality improvement program database. World J Surg. 2019;43(3):937–43.

27. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014;20(24):7864–77.
28. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database Syst Rev. 2016;7:CD009323.
29. Jayakrishnan TT, Nadeem H, Groeschl RT, George B, Thomas JP, Ritch PS, et al. Diagnostic laparoscopy should be performed before definitive resection for pancreatic cancer: a financial argument. HPB. 2015;17(2):131–9.
30. Morris S, Gurusamy KS, Sheringham J, Davidson BR. Cost-effectiveness of diagnostic laparoscopy for assessing resectability in pancreatic and periampullary cancer. BMC Gastroenterol. 2015;15:44.
31. Memba R, Conlon KC. Laparoscopic staging for pancreatic cancer. In: Minimally invasive surgery of the pancreas. New York, NY: Springer; 2018. p. 75–89.
32. Network NCC. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma. Version 1 2018. Plymouth Meeting, PA: NCCN; 2019. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed 7 Nov 2019.
33. Hasson HM. A modified instrument and method for laparoscopy. Am J Obstet Gynecol. 1971;110(6):886–7.
34. Doyle M, Pratt WB. Intraoperative diagnostic techniques. In: Jarnagin W, editor. Blumgart's surgery of the liver biliary tract and pancreas, vol. 1. Amsterdam: Elsevier; 2012. p. 369–75.
35. Conlon KC, Gallagher TK. Laparoscopic staging and approaches to cancer. Maingot's abdominal operations. 12th ed. New York, NY: McGraw-Hill; 2013. p. 75–95.
36. Ganta SV, Conlon KC. Laparoscopic staging for pancreatic carcinoma. In: Greene F, Heniford BT, editors. Minimally invasive cancer management. New York, NY: Springer; 2001. p. 123–30.
37. Conlon KC, Johnston SM. Laparoscopic staging of periampullary neoplasms. In: Clavien P-A, editor. Atlas of upper gastrointestinal and hepato-pancreato-biliary surgery. New York, NY: Springer; 2007. p. 917–27.

Chapter 53
Standard Pancreatoduodenectomy for Resectable Pancreatic Cancer

Lukasz Filip Grochola, Nico Seeger, Stefan Stättner, Kjetil Søreide, and Stefan Breitenstein

Take Home Messages

- Pancreaticoduodenectomy is a complex procedure consisting of an *exploratory phase,* a *resection phase* and a *reconstruction phase*, each with several important steps to consider.
- The exploratory phase consists of duodenal mobilization, identification of the SMV/PV confluence, dissection in the hepatoduodenal ligament with cholecystectomy and a proper lymphadenectomy, as well as exclusion of an infiltration of any major arteries. This phase ensures resectability before the point of no return is reached during the operation.
- The resection phase includes the division of the common bile duct, transection of the duodenum and pancreas with division of the mesopancreas and specimen removal.
- Reconstruction is done between the enteric tract and the pancreatic stump, the transected bile duct as well as the duodenal (or gastric) remnant.
- Several reconstructive techniques and variations have been described, e.g. for the pancreato-enteric anastomosis, with no consensus on the preferred type of reconstruction.

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- Some variations are suggested (e.g. dunking technique) for when the pancreatic gland is soft and the pancreatic duct small and, hence, an increased risk of pancreatic leak may be mitigated.

Pearls and Pitfalls

- Important anatomic variants must be declared prior to surgery, such as a replaced right or common hepatic artery which originates from the SMA and is typically located lateral and posterior to the common bile duct.
- Stenosis of the coeliac trunk should be detected at the time of preoperative imaging and its patency restored before pancreaticoduodenectomy.
- The gastroduodenal artery is the most frequent location of postoperative pseudoaneurysms secondary to pancreatic fistula. It is important to ligate the vessel with a carefully placed non-absorbable suture and a metal clip which can aid in finding the position of the stump by interventional radiology, should a bleeding occur in the postoperative course.
- The medial and posterior margins are the most common site of R1 resections. When transection of the mesopancreas is performed, the anterolateral aspect of the SMA should be carefully exposed in order to increase the chance of achieving tumor-free margins.
- No specific surgical technique can eliminate the risk of complications, such as clinically relevant postoperative pancreatic fistula.

Future Perspectives

- Investigations into how various surgical techniques may have an effect on function and outcomes may be needed, also with increasing use of neoadjuvant chemotherapy.
- Novel investigations that may predict patency or risk to the pancreatoenteric anastomosis would be useful if clinically applicable and easy to use for surgeons.
- When to use drains, which type (internal, external, abdominal) and how long to keep them will continue to be a matter of intensive debate.

53.1 Introduction

Pancreatic ductal adenocarcinoma is predominantly localized within the pancreatic head and is markedly the most prevalent tumor of the pancreas followed by other periampullary neoplasms that originate in either the Ampulla of Vater, in the common bile duct or in the duodenum. For pancreatic head cancer, a pancreatoduodenectomy offers at present the only chance for a cure. The procedure still carries a significant morbidity and mortality risk and results in varying oncologic outcomes

[1–4]. A meticulous surgical technique, proper patient selection, comprehensive perioperative care as well as multimodal treatment approaches are key to achieving optimal clinical and oncologic outcomes [1, 5].

Over the past century, since the first reports of successful pancreatoduodenectomy performed in two stages by the surgeons Kausch in 1909 and Tenani in 1922 [6, 7], the procedure has evolved remarkably. It was first popularized by Allen Whipple who in 1941 reported 41 cases with a historically relatively low mortality rate of 27%, after he performed the operation in one stage [8]. Numerous successive technical advances, centralization of pancreatic surgery and improvements in intensive care have helped to gradually reduce morbidity and mortality to 30–50% and 2–3%, respectively [9, 10]. Together, these advances eventually led to a far-reaching acceptance of this operation.

While the procedure is entertained both laparoscopically and robotically (covered in other chapters in this book) as well as in more advanced disease (e.g. involving resection of veins and arteries), this chapter will focus on the open technique, describing the essential steps and variations for performing a safe resection of the pancreatic head cancer. Pre-operative work-up with state-of-the at imaging, patient selection and pre-operative counseling and informed consent is mandatory (Box 53.1).

Box 53.1 Pre-operative Items to Consider

- The precise evaluation of local tumour relationships relative to major vascular structures (superior mesenteric/portal vein, superior mesenteric artery, hepatic arteries and coeliac artery) with a computed tomography (CT) using a contrast-enhanced pancreas protocol serves as the basis for the classification of individual tumours without detectable metastases as resectable, borderline resectable and locally advanced, and is designed to guide therapeutic decisions [5, 11].
- Appropriate patient selection involves the evaluation of patient age and performance status. Patients above the age of 80 and those with a Charlson Age-Comorbidity Index above 4 have a relatively high risk of in-hospital death [9].
- Endoscopic decompression of the bile duct is indicated in patients who present with cholangitis or borderline resectable patients who are scheduled for neoadjuvant treatment. However, it should be avoided in patients who present with obstructive jaundice without cholangitis, because the procedure can lead to an acute pancreatitis or infectious complications [12].
- Nutritional status, which can be assessed using patient's weight loss and body mass index as part of the routine preoperative work-up, should be corrected perioperatively in order to lower the risk for surgery-related complications [13].
- An effective treatment of iron deficiency, which is the most common cause of pre-operative anaemia, is recommended in order to reduce the need for transfusions and potentially improve outcomes [14].

53.2 The Procedure

A pancreatoduodenectomy is a complex procedure, best described by breaking it into several steps, with three major phases which are the *exploratory phase*, the *resection phase* and the *reconstruction phase*. Each phase will be described with the associated steps, in which standard accepted techniques will be proposed with existing alternatives, when felt of importance. Notably, there is a huge variation of each step and alternatives, and an exhaustive overview is not possible, but relevant references will give direction to further details, where appropriate.

Every procedure starts with going through the WHO Surgical Safety checklist [15]. Items of particular importance to the specific patient and procedure of the days should be highlighted to the team in order to facilitate maximum safety and understanding of the plan at hand.

53.3 Exploratory Phase

The patient is placed in the supine position. A Chevron/rooftop or an upper abdominal midline incision is performed, the round and falciform ligaments are divided and a bilateral retractor frame is set up. The liver and all peritoneal surfaces should be inspected for cancer deposits and distant metastases and any suspicious lesions should be biopsied and sent for frozen section to avoid a futile procedure in case of disseminated disease.

53.3.1 Mobilization of Duodenum

The lesser sac is entered through the gastrocolic ligament, which is divided to the right. The right colonic flexure is mobilized and a wide Kocher maneuver is performed to evaluate the local tumor relationship relative to the superior mesenteric artery (SMA) in the retroperitoneum (Fig. 53.1). This maneuver exposes the ligament of Treitz, which is divided and allows for the early inspection of the SMA, which is dissected on its right hemi-circumference. This so-called posterior "artery first approach" helps exclude any tumor infiltration of this artery at an early stage during the operation where CT cannot rule out involvement since arterial encasement of the SMA (as well as of the hepatic arteries or celiac axis) is generally accepted as a contraindication to resection [16, 17]. In fact, at least six artery-first approaches to pancreatoduodenectomy have been described in the literature [17]. Other suggested benefits of this approach include improved R0 resection rates along the SMA margin, improved overall survival, a reduction in intraoperative blood loss and lower overall morbidity rates [16].

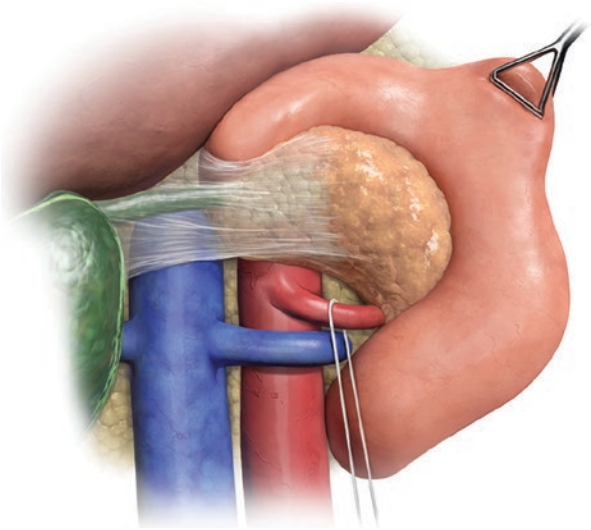

Fig. 53.1 Kocher maneuver with an "artery first approach". The depicted wide Kocher maneuver serves to mobilise the pancreatic head and the duodenum off the retroperitoneum and evaluate the local tumor relationship relative to the superior mesenteric artery

53.3.2 Identification of the SMV

Next, the transverse mesocolon is mobilized from the anterior surface of the pancreatic head to expose the superior mesenteric vein (SMV) at the inferior margin of the pancreatic neck, where the vessel continues its course behind the pancreas and can be assessed for tumor involvement together with the portal vein (PV). In general, the resection and reconstruction of these veins is feasible if deemed necessary due to invasive cancer growth. However, special attention should be paid to the involvement of the first jejunal branches of the SMV, since even a short segment infiltration at this level may preclude a safe reconstruction of this crucial vessel. In such a case, it is advisable to deem the tumor unresectable rather then proceed with the resection, which could otherwise lead to an acute hemorrhagic infarction of the small bowel. In contrast, involvement of the middle colic vein or artery does not prevent resection since they may be taken with the specimen, without compromising the blood supply to the transverse colon.

53.3.3 Dissection in Hepatoduodenal Ligament

Attention is then turned to the hepatoduodenal ligament and the hepatic arteries to ensure resectability. Cholecystectomy is performed in a typical fashion, even if the operation is abandoned in the later course, to avoid potential problems. The cystic

duct is traced to its origin from the common bile duct (CBD), which is best dissected in the hepatoduodenal ligament from left to right (Fig. 53.2a), which helps avoid injury to the portal vein. Another pitfall is an injury to a fully replaced right or common hepatic artery, which originates in the SMA and is typically located lateral and posterior to the common bile duct (Fig. 53.2b). Importantly, such variant should also be clearly visible with state-of-the-art preoperative imaging and therefore the surgeon should not be caught off guard. An accessory right hepatic artery, which can be found in the same location as a fully replaced artery but in the presence of a native right hepatic artery, should also be preserved. However, if necessary, such an accessory right hepatic artery can be ligated without the need for reconstruction in the presence of a patent native right hepatic artery.

Next, the gastroduodenal artery (GDA) is identified and clamped with a bulldog clamp to test if the flow in the hepatic artery depends on the GDA, which indicates a partial or complete occlusion of the coeliac trunk. In case of a weak pulse in the hepatic artery at test clamping, division of the median arcuate ligament may restore the flow in the celiac trunk. Again, a stenosis of the coeliac trunk should be visible with state-of-the-art preoperative imaging and its patency should be restored before

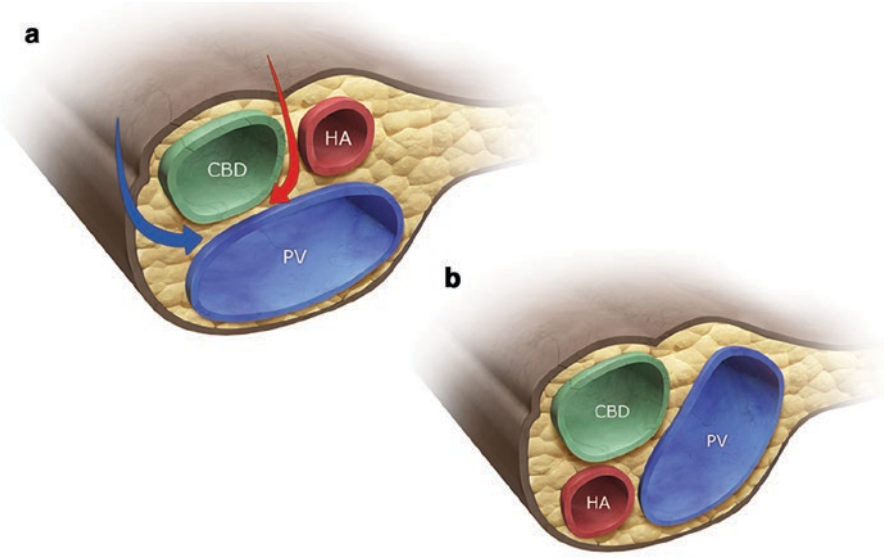

Fig. 53.2 Dissection in the hepatoduodenal ligament. The hepatoduodenal ligament with its three main anatomic structures hepatic artery (HA), portal vein (PV) and common bile duct (CBD) is shown. (**a**) Standard anatomy where the HA is located to the left of the CBD. The CBD is best encircled by dissecting in the plane between the HA and the CBD (red arrow). An additional dissection in the plane between the CBD and PV (blue arrow) can be helpful but must be performed very cautiously to avoid an injury to the PV. (**b**) A frequent anatomic variant is shown with a replaced HA that originates from the superior mesenteric artery and is usually located to the right and posterior to the CBD

pancreaticoduodenectomy ideally using endovascular techniques. After confirming an adequate pulse in the proper hepatic artery and having already excluded an infiltration of the hepatic arteries, the coeliac trunk and the SMA by the tumour, as well as a non-reconstructable involvement of the SMV-PV axis, the surgeon can now proceed to the resection phase.

53.4 Resection Phase

The GDA is ligated and divided. Since the GDA is the most frequent location of postoperative pseudoaneurysms, it is important to ligate the vessel with a carefully placed non-absorbable suture and a metal clip which can aid in finding the position of the stump should a bleeding occur in the postoperative course [18]. The right gastric artery is usually ligated but can be preserved if post pyloric reconstruction is planned, making lymph node dissection technically more challenging. The CBD is transected cephalic to the origin of the cystic duct while leaving the bifurcation into the left and right hepatic duct intact. Microbial swabs should be taken at this point to get information on potential microbiota contaminating the bile. Great care should be taken to avoid injury to the right hepatic artery, which is normally located directly behind the common hepatic duct at this level. At this stage, a lymphadenectomy of the hepatoduodenal ligament with removal of all fatty tissues is recommended [19], which exposes the suprapancreatic portion of the PV and facilitates the creation of a tunnel between the SMV-PV and the pancreatic neck.

53.4.1 Transsection of the Duodenum and Pancreas

The right gastroepiploic artery and vein are divided, and the duodenum is transsected approximately 2–3 cm beyond the pylorus using a linear stapler. If the tumor infiltrates the first portion of the duodenum or the pylorus and pyloric preservation is not feasible, a distal gastrectomy is performed instead. The neck of the pancreas is looped in a typical avascular plane with a nylon tape to avoid injury to the anterior portion of the PV during transection which is usually done with an electrocautery or scalpel [20, 21]. To decrease the development of pancreatic fistula from the transection surface, various alternative methods have been attempted for pancreas transection, including the use of ultrasonically activated shears/scalpel [21, 22], the cavitron ultrasonic surgical aspirator [23] and crush-clamping [24]. Those transection techniques were only evaluated in mostly small, one-arm, single-institutional studies and delivered mixed results, and therefore cannot be recommended as standard procedures for pancreatic transection at this stage. Bleeding vessels from the transected pancreas are best ligated using 5/0–6/0 non-absorbable sutures. Narrowing of the pancreatic duct should be meticulously avoided. Electrical cautery on the pancreas for hemostasis should be kept to a minimum since it is a widely held belief that

extensive application of electrical cautery on the pancreas may be detrimental to the tissues and compromise the pancreato-enteric reconstruction. A frozen section of the pancreatic remnant can be sent for histology to test for tumor free margins at this stage of the operation or later.

53.4.2 Division of the Mesopancreas

The jejunum is divided using a linear stapler approximately 15–20 cm distal to the Treitz ligament. The mesentery is divided at its entry point to the proximal jejunal loop, which is passed together with the fourth portion of the duodenum posterior to the mesenteric vessels to the right of the operative field. The head and uncinate process can now be separated from the superior mesenteric vessels, whereby the mesopancreas (Box 53.2) [25–27] is divided along the superior mesenteric artery with ligatures, bipolar cautery, clips or energy-based devices (e.g. Thunderbeat™ or Harmonic™ shears). Stapling off the entire resection surface with a stapler is not recommended due to the high risk of vessel injury. Special care should be taken when performing this step to expose the anterolateral aspect of the SMA while avoiding injury to this crucial vessel in order to ensure that all soft tissues along the superior mesenteric vessels are harvested, since the medial and posterior margins are the most common site of R1 resections [28].

Box 53.2 The Mesopancreas
The term mesopancreas refers to retropancreatic tissue, which consists of areolar and adipose tissue, peripheral nerves, blood and lymphatic vessels or capillaries, as well as lymph nodes. There is no fibrous sheath or fascia surrounding these structures and therefore does not have well defined boundaries. Rather, the mesopancreas is continuous and connected through its components with the paraaortic area, in line with the concept that considers the retropancreatic area as an anatomical site of embryologic fusion of peritoneal layers, the so called “Treitz fusion fascia”.

If venous reconstruction is required (covered in detail in a separate chapter in this book), it is reserved as the last step in the resection phase. Primary anastomosis can be done for a short segment vein resection (≤2–3 cm). To this end, adequate mobilization and control of the proximal and distal PV and SMV must be ensured using vessel loops for gentle dissection and control. In addition, a mobilization of the liver may help to approximate both ends of the resected vein. For long segment reconstruction, interposition grafts are used, such as the internal jugular vein (Fig. 53.3). The specimen is sent for histologic examination, frozen section of the pancreatic

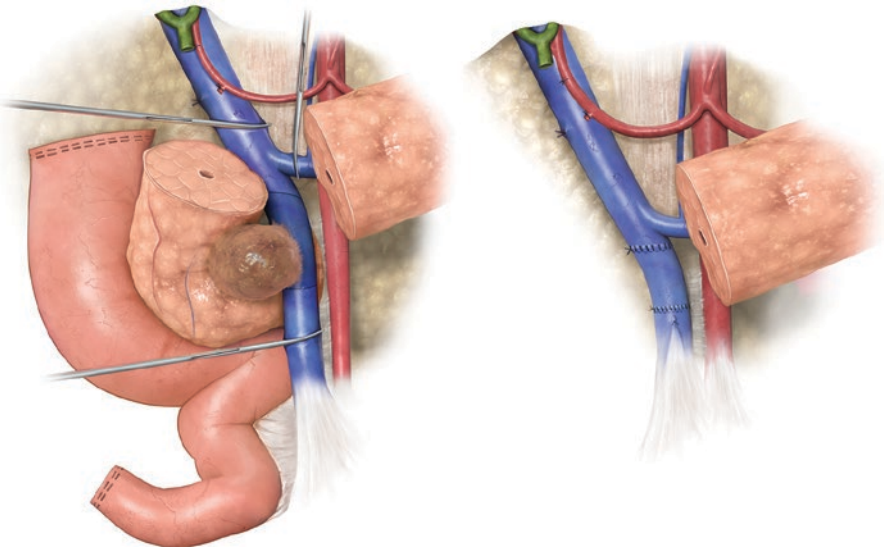

Fig. 53.3 Last step of the resection phase. The specimen consists of the first portion of the duodenum or distal stomach, neck, head, and uncinate process of the pancreas, distal biliary tree, and approximately 10–20 cm of the proximal jejunum (the gallbladder is already removed). Here a pancreatic carcinoma in the head of the pancreas that infiltrates the superior mesenteric vein but is amenable to reconstruction is shown. Venous reconstruction is performed at the end of the resection phase. If primary anastomosis is not feasible in case of long segment vein resections (>2–3 cm), interposition grafts are used as shown

stump and the distal CBD are requested at this time, hemostasis is ensured and the operative field washed with saline solution before proceeding to the reconstruction phase.

53.4.3 Standard lymphadenectomy

Lymph node (Ln) dissection, which is an integral part of the above-described resection phase, is best performed in line with the consensus statement by the International Study Group on Pancreatic Surgery (ISGPS) [19]. According to the nomenclature of the Japanese Pancreas Society [29] standard lymphadenectomy for pancreatoduodenectomy sshould include Ln stations number 5 (suprapyloric Ln), 6 (infrapyloric Ln), 8a (Ln in the anterosuperior group along the common hepatic artery), 12b (Ln along the bile duct), 12c (Ln around the cystic duct), 13a (Ln on the posterior aspect of the superior portion of the head of the pancreas), 13b (Ln on the posterior aspect of the inferior portion of the head of the pancreas), 14a/b (Ln stations along the right side of the SMA), 17a (Ln on the anterior surface of the superior portion of the head of the pancreas), and 17b (Ln on the anterior surface of the inferior portion of the head of the pancreas) [19]. A standard lymphadenectomy should regularly provide

≥15 Ln's to ensure adequate pathologic staging of the disease [19]. Extended lymphadenectomy, which includes dissection of additional Ln stations cannot be recommended because the actual survival benefit is limited at best [19, 30–33].

53.5 Reconstruction Phase

The reconstruction phase ensures that continuity is maintained between the pancreatic stump, biliary tract and duodenal/stomach stump to the enteric tract by appropriate anastomoses. Notably, several variants and techniques are described and used for each of the three anastomoses (the pancreato-enteric, hepaticojejunostomy and entero-enteric anastomosis). We will describe essential and accepted techniques and refer to variations where applicable.

53.5.1 Pancreato-Enteric Anastomosis

According to a recent position statement by the International Study Group of Pancreatic Surgery (ISGPS), there is currently no clear consensus regarding the ideal method of pancreatico-enteric anastomosis, which includes over 60 different types of pancreaticojejunostomy and pancreaticogastrostomy [34–38].

Despite numerous trials that compared diverse pancreatico-enteric anastomosis techniques and other adjunctive strategies (pancreatic duct stenting, somatostatin analogues, etc.), no specific technique can eliminate the development of clinically relevant postoperative pancreatic fistula, which remains the most troublesome complication after pancreatoduodenectomy [34–38]. The two most commonly used methods to establish drainage of the pancreatic remnant to the gastrointestinal tract (with similar reported rates of pancreatic fistulas) are both variations of the pancreato-jejunal anastomosis, the so-called *dunking* procedure and the *duct-to-mucosa* technique [34, 39].

For both techniques, the pancreatic remnant is mobilized from the retroperitoneum and splenic vein for a distance of approximately 1.5–2 cm to facilitate suture placement for the pancreato-enteric anastomosis. The transected jejunum is delivered to the supra-mesenteric compartment either through an opening in the transverse mesocolon to the right of the middle colic vessels or in the bed of the resected duodenum. The antimesenteric jejunal border is brought alongside the cut end of the pancreas 2–3 cm distal to the staple line at the proximal end of the jejunum and the anastomosis is performed in an end-to-side fashion.

53.5.2 Duct-to-Mucosa *Pancreato-Jejunal Anastomosis*

First, a back outer row of interrupted monofilament absorbable sutures (4–0 or 5–0 PDS) is placed through the dorsal capsule, with the needle entering the pancreatic parenchyma approximately 1 cm from the cut end of the stump taking an

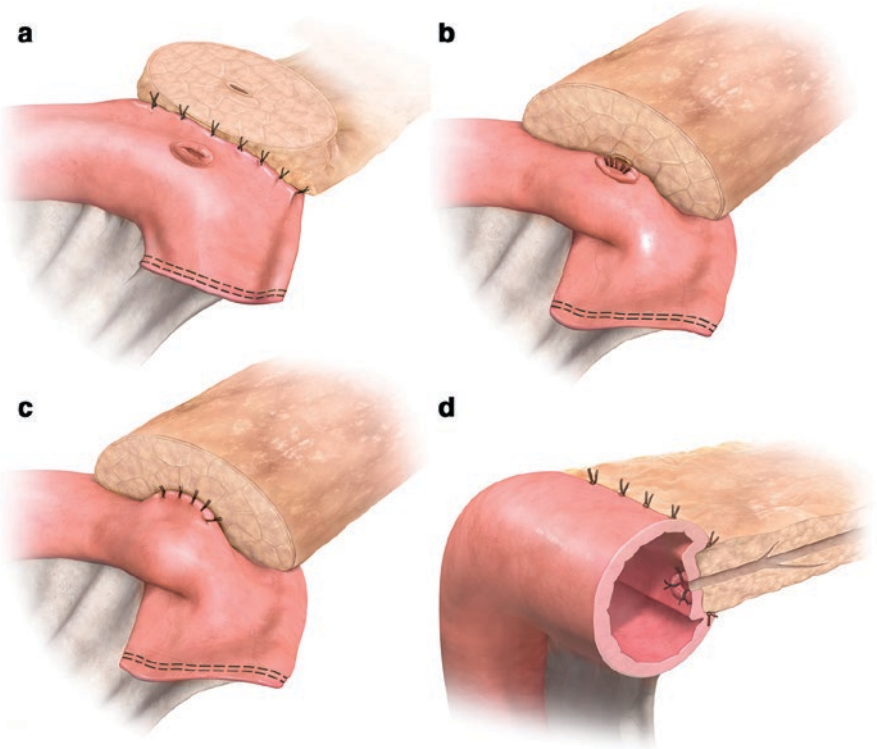

Fig. 53.4 Duct-to-mucosa pancreato-jejunal anastomosis. (**a**) Completed outer posterior row with interrupted sutures. (**b**) Posterior inner row of the anastomosis with careful adaptation of the duct to the jejunal opening. (**c**) Anterior inner row. (**d**) Completed anastomosis

adequate bite of the tissue and a seromuscular bite of the jejunum (Fig. 53.4a). Knots are only tied following completion of each of the four suture rows and a careful technique is used to avoid tearing the pancreatic parenchyma. Next, the pancreatic duct is identified and a small jejunotomy corresponding to the duct is created using electrocautery. The posterior inner row of the anastomosis is then constructed using 5–0 or 6–0 PDS sutures, taking generous bites of the pancreatic parenchyma with the duct and full-thickness bites of the jejunum (Fig. 53.4b). If the pancreatic duct is small (1–2 mm in diameter), a total of three sutures will suffice. For larger pancreatic ducts, the sutures are spaced about 1.0–1.5 mm apart, and more sutures can be required to adapt the duct to the jejunal mucosa. This step is followed by the anterior inner row of 4–0/5–0 PDS sutures, which is driven through the pancreatic parenchyma ensuring an adequate bite of the tissue of the pancreas and the anterior enterotomy edge (Fig. 53.4c). Great care should be taken to avoid catching the back wall of the duct and thus occluding the pancreatic duct lumen. A second row of anterior sutures (4–0/5–0 PDS) is finally placed through the ventral capsule and the seromuscular layer of the jejunal limb at a point that will allow a fold of the jejunal wall to cover the inner row of sutures in a tension-free manner (Fig. 53.4c, d).

53.5.3 *Dunking Procedure Pancreato-Jejunal Anastomosis (Invagination Technique)*

Another widely adopted variation of the pancreato-jejunal anastomosis is the *dunking procedure*, which allows the jejunum to be pulled over the pancreas more prominently than in the *duct-to-mucosa* anastomosis. First, a back outer row of 3–0 silk mattress sutures is placed about 5–10 mm back from the edge of the pancreas, beginning at the superior pancreatic margin and extending to the inferior border of the pancreas (Fig. 53.5a). A longitudinal enterotomy is then performed with the width of the opening tailored to the size of the pancreatic stump. For the inner posterior layer, two 3–0 Vicryl sutures are placed at the inferior edge of the anastomosis (Fig. 53.5b). The needle is then driven through the cut face of the pancreas first catching about one-third of the surface, ensuring an adequate bite of the parenchyma and exiting just at the cut edge of the remnant pancreas. The bite is carried into the lumen of the jejunum in a single pass incorporating the full thickness of

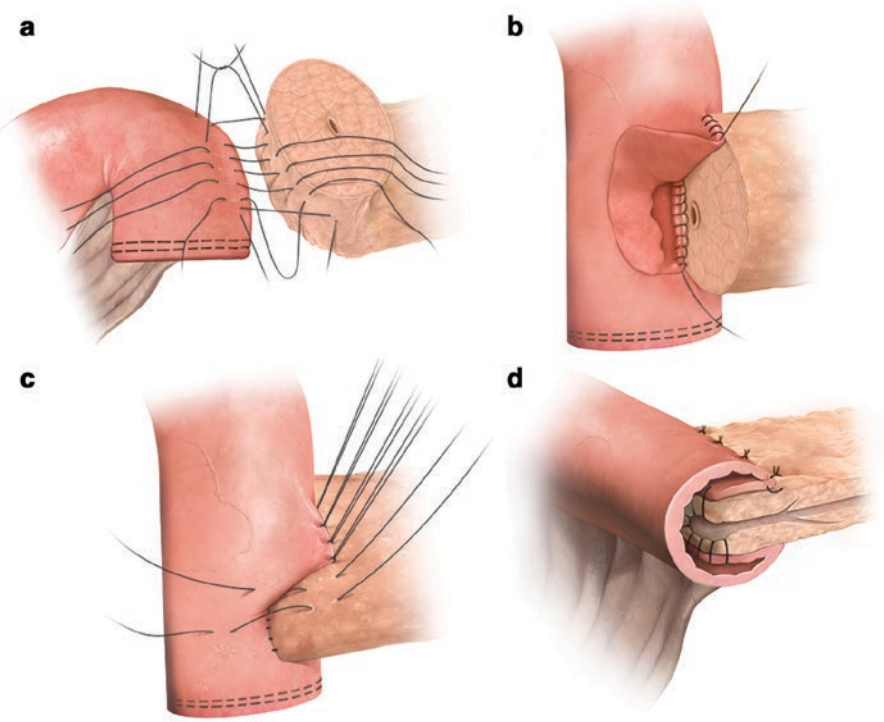

Fig. 53.5 Pancreato-jejunal anastomosis: dunking procedure. (**a**) Outer layer of posterior row with interrupted mattress sutures. (**b**) Inner continuous sutures; the posterior row with locking stitches is depicted dorsally. (**c**) Outer layer of anterior row. (**d**) Completed anastomosis with invagination of the pancreatic remnant

jejunum. A running suture using locking stitches is placed along the posterior inner row starting at the lower border of the gland and advancing to the superior margin of the anastomosis. When the pancreatic duct is large, the stitches may be placed into it, thereby incorporating the duct into the posterior inner row. In case of a small duct, however, placing the stitches into the duct may be omitted altogether. Next, the ventral row of the inner layer is created in a running, nonlocking fashion, entering the anterior surface of the pancreas and exiting one-third of the way down the cut face of the pancreas, again ensuring a full-thickness bite of the jejunum (Fig. 53.5b). After completion, the anterior inner suture row is tied to the inner posterior suture from the back row. Lastly, a ventral outer layer of 3/0 silk mattress sutures is placed ensuring an adequate bite of the pancreatic parenchyma (Fig. 53.5c). A seromuscular bite of the jejunum is taken at a point that will allow a fold of the jejunal wall to cover the inner row of sutures (Fig. 53.5c, d). All knots are gently tied after completion of this suture row.

53.5.4 Bilioenteric Anastomosis

In contrast to the pancreatoenteric anastomosis, the approach to the biliary anastomosis is less variable. The bilioenteric anastomosis is usually constructed approximately 10–15 cm downstream from the pancreato-jejunostomy in an end-to-side fashion with a single layer of PDS 5/0 sutures. The cut edge of the bile duct is freshened to obtain well-perfused healthy tissues and a small enterotomy is made at the antimesenteric border of the jejunal loop. The posterior suture layer is first constructed by placing the sutures inside out both on the jejunum and on the hepatic duct, leaving the knot outside the anastomosis, although variations of this technique exist which leave the knots inside. Each individual suture is held in clamps, until the entire suture row is completed and before knotting begins. Alternatively, this anastomosis can be performed in a running fashion when the bile duct is significantly enlarged. Lastly, the anterior suture row is completed in a similar fashion with knots outside. After completion of the anastomosis, the mesocolic opening around the jejunal limb or the Treitz ligament are closed to avoid an internal hernia.

53.5.5 Reconstruction of Gastrointestinal Continuity

This reconstruction involves either an end-to-side gastrojejunostomy or duodenojejunostomy depending on whether a classic or pylorus-preserving pancreatoduodenectomy is performed. Current evidence shows no relevant differences in mortality, morbidity and survival between both techniques, although some data suggest that operating time, intraoperative blood loss and the need for blood transfusions may be more favorable with the pylorus-preserving operation [40–42]. The gastro- and duodenojejunostomies are both made approximately 50 cm downstream of the

hepaticojejunostomy in an end-to-side fashion in one or two layers using a PDS 4/0 running or interrupted sutures. The reconstruction can be done either in a retrocolic or antecolic fashion with similar postoperative outcomes as demonstrated by multiple randomized controlled trials and meta-analyses [43–47]. The placement of two closed suction drains (Box 53.3) at the pancreatic and biliary anastomoses allows for early detection of a postoperative pancreatic fistula (POPF) and, should POPF develop, drainage of pancreatic effluent, thereby mitigating the clinical severity and morbidity of the fistula [48, 49].

Box 53.3 Post-operative Items to Consider

- Routine placement of drains at the pancreatic and biliary anastomoses significantly reduces the incidence of gastroparesis, intra-abdominal fluid collections and the severity of postoperative complications [48].
- In patients with low risk of pancreatic fistula, the drains can be safely removed by the third postoperative day after standard pancreatic resections [49–51]. A prolonged period of drain insertion in the absence of a pancreatic fistula is associated with a higher rate of postoperative complications, a longer hospital stay and increased costs [50].
- Routine prolonged nasogastric (NG) decompression is unnecessary and NG suction tubes are immediately removed at extubation [52].
- Postoperative early resumption of oral intake is safe and should be endorsed within enhanced recovery protocols [13]. In case of severe postoperative complications or poor tolerance of oral food after the operation, supplementary artificial nutrition should be started instantly [13]. When artificial nutritional support is needed, the enteral route is whenever possible preferred over parenteral nutrition [13].

53.6 Conclusions

Pancreaticoduodenectomy is a complex procedure that requires a meticulous surgical technique and an appropriate patient selection in order to achieve low morbidity and mortality rates. A detailed radiological evaluation and intraoperative exploration will avoid that the surgeon is caught off guard due to an unexpected infiltration of major vascular structures or the presence of anatomic variants, in particular those of hepatic arteries. Several techniques for the various steps of the procedure have been described, but more so than the choice of the techniques used, a successful operation is most dependent on the surgeon's concentration on careful and precise execution of the chosen technique.

References

1. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371(22):2140–1.
2. Lennon AM, Wolfgang CL, Canto MI, Klein AP, Herman JM, Goggins M, et al. The early detection of pancreatic cancer: what will it take to diagnose and treat curable pancreatic neoplasia? Cancer Res. 2014;74(13):3381–9.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
4. Dimitrakopoulos C, Vrugt B, Flury R, Schraml P, Knippschild U, Wild P, et al. Identification and validation of a biomarker signature in patients with resectable pancreatic cancer via genome-wide screening for functional genetic variants. JAMA Surg. 2019;154(6):e190484.
5. Heestand GM, Murphy JD, Lowy AM. Approach to patients with pancreatic cancer without detectable metastases. J Clin Oncol. 2015;33(16):1770–8.
6. Kausch W. Das Carcinom der Papilla duodeni und seine radikaleEntfernung. In: Von Schmiedebach H-P, Winau R, Häring R, editors. Erste Operationen Berliner Chirurgen 1817–1931. Berlin: De Gruyter; 2015. p. 40–51.
7. Tenani O. Contributo alla chirurgia della papilla del Vater. Policlinico. 1922;29:291–333.
8. Whipple AO. The rationale of radical surgery for cancer of the pancreas and ampullary region. Ann Surg. 1941;114(4):612–5.
9. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015;220(4):530–6.
10. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA, et al. 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. HPB (Oxford). 2014;16(1):83–90.
11. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(8):1028–61.
12. Povoski SP, Karpeh MS, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg. 1999;230(2):131–42.
13. Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018;164(5):1035–48.
14. Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how? Anaesthesia. 2019;74(Suppl 1):49–57.
15. Safety WAfP. WHO surgical safety checklist and implementation manual. Geneva: WHO; 2008. https://www.who.int/patientsafety/safesurgery/ss_checklist/en/.
16. Ironside N, Barreto SG, Loveday B, Shrikhande SV, Windsor JA, Pandanaboyana S. Meta-analysis of an artery-first approach versus standard pancreatoduodenectomy on perioperative outcomes and survival. Br J Surg. 2018;105(6):628–36.
17. Sanjay P, Takaori K, Govil S, Shrikhande SV, Windsor JA. 'Artery-first' approaches to pancreatoduodenectomy. Br J Surg. 2012;99(8):1027–35.
18. Puppala S, Patel J, McPherson S, Nicholson A, Kessel D. Hemorrhagic complications after Whipple surgery: imaging and radiologic intervention. AJR Am J Roentgenol. 2011;196(1):192–7.
19. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
20. Yamaue H, Tani M, Kawai M, Hirono S, Okada K, Miyazawa M. Pancreatic dissection in the procedure of pancreaticoduodenectomy (with videos). J Hepatobiliary Pancreat Sci. 2012;19(2):95–9.

21. Takahashi S, Gotohda N, Kato Y, Konishi M. Measure of pancreas transection and postoperative pancreatic fistula. J Surg Res. 2016;202(2):276–83.
22. Okabayashi T, Hanazaki K, Nishimori I, Sugimoto T, Yoshioka R, Dabanaka K, et al. Pancreatic transection using a sharp hook-shaped ultrasonically activated scalpel. Langenbeck's Arch Surg. 2008;393(6):1005–8.
23. Sugiyama M, Abe N, Izumisato Y, Tokuhara M, Masaki T, Mori T, et al. Pancreatic transection using ultrasonic dissector in pancreatoduodenectomy. Am J Surg. 2001;182(3):257–9.
24. Koga R, Yamamoto J, Saiura A, Natori T, Katori M, Kokudo N, et al. Clamp-crushing pancreas transection in pancreatoduodenectomy. Hepato-Gastroenterology. 2009;56(89):89–93.
25. Peparini N, Chirletti P. Mesopancreas: a boundless structure, namely R1 risk in pancreaticoduodenectomy for pancreatic head carcinoma. Eur J Surg Oncol. 2013;39(12):1303–8.
26. Agrawal MK, Thakur DS, Somashekar U, Chandrakar SK, Sharma D. Mesopancreas: myth or reality? JOP. 2010;11(3):230–3.
27. Peparini N. Mesopancreas: a boundless structure, namely the rationale for dissection of the paraaortic area in pancreaticoduodenectomy for pancreatic head carcinoma. World J Gastroenterol. 2015;21(10):2865–70.
28. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008;15(6):1651–60.
29. Japan Pancreas Society. Classification of pancreatic carcinoma. 2nd English ed. Tokyo: Kanehara & Co. Ltd; 2003.
30. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–66. discussion 66–8
31. Riall TS, Cameron JL, Lillemoe KD, Campbell KA, Sauter PK, Coleman J, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma—part 3: update on 5-year survival. J Gastrointest Surg. 2005;9(9):1191–204; discussion 204–6.
32. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–28; discussion 28–30.
33. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci. 2012;19(3):230–41.
34. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. Pancreatic anastomosis after pancreatoduodenectomy: a position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161(5):1221–34.
35. Daamen LA, Smits FJ, Besselink MG, Busch OR, Borel Rinkes IH, van Santvoort HC, et al. A web-based overview, systematic review and meta-analysis of pancreatic anastomosis techniques following pancreatoduodenectomy. HPB (Oxford). 2018;20(9):777–85.
36. Hua J, He Z, Qian D, Meng H, Zhou B, Song Z. Duct-to-mucosa versus invagination pancreaticojejunostomy following pancreaticoduodenectomy: a systematic review and meta-analysis. J Gastrointest Surg. 2015;19(10):1900–9.
37. Lyu Y, Li T, Cheng Y, Wang B, Chen L, Zhao S. Pancreaticojejunostomy versus pancreaticogastrostomy after pancreaticoduodenectomy: an up-to-date meta-analysis of RCTs applying the ISGPS (2016) criteria. Surg Laparosc Endosc Percutan Tech. 2018;28(3):139–46.
38. Wang W, Zhang Z, Gu C, Liu Q, Liang Z, He W, et al. The optimal choice for pancreatic anastomosis after pancreaticoduodenectomy: a network meta-analysis of randomized control trials. Int J Surg. 2018;57:111–6.

39. Crippa S, Cirocchi R, Randolph J, Partelli S, Belfiori G, Piccioli A, et al. Pancreaticojejunostomy is comparable to pancreaticogastrostomy after pancreaticoduodenectomy: an updated meta-analysis of randomized controlled trials. Langenbeck's Arch Surg. 2016;401(4):427–37.
40. Hüttner FJ, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Büchler MW, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev. 2016;2:CD006053.
41. Karanicolas PJ, Davies E, Kunz R, Briel M, Koka HP, Payne DM, et al. The pylorus: take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. Ann Surg Oncol. 2007;14(6):1825–34.
42. Wu W, Hong X, Fu L, Liu S, You L, Zhou L, et al. The effect of pylorus removal on delayed gastric emptying after pancreaticoduodenectomy: a meta-analysis of 2,599 patients. PLoS One. 2014;9(10):e108380.
43. Tamandl D, Sahora K, Prucker J, Schmid R, Holst JJ, Miholic J, et al. Impact of the reconstruction method on delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: a prospective randomized study. World J Surg. 2014;38(2):465–75.
44. Bell R, Pandanaboyana S, Shah N, Bartlett A, Windsor JA, Smith AM. Meta-analysis of antecolic versus retrocolic gastric reconstruction after a pylorus-preserving pancreatoduodenectomy. HPB (Oxford). 2015;17(3):202–8.
45. Eshuis WJ, van Eijck CH, Gerhards MF, Coene PP, de Hingh IH, Karsten TM, et al. Antecolic versus retrocolic route of the gastroenteric anastomosis after pancreatoduodenectomy: a randomized controlled trial. Ann Surg. 2014;259(1):45–51.
46. Gangavatiker R, Pal S, Javed A, Dash NR, Sahni P, Chattopadhyay TK. Effect of antecolic or retrocolic reconstruction of the gastro/duodenojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled trial. J Gastrointest Surg. 2011;15(5):843–52.
47. Joliat GR, Labgaa I, Demartines N, Schäfer M, Allemann P. Effect of antecolic versus retrocolic gastroenteric reconstruction after pancreaticoduodenectomy on delayed gastric emptying: a meta-analysis of six randomized controlled trials. Dig Surg. 2016;33(1):15–25.
48. Van Buren G, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg. 2014;259(4):605–12.
49. Villafane-Ferriol N, Shah RM, Mohammed S, Van Buren G, Barakat O, Massarweh NN, et al. Evidence-based management of drains following pancreatic resection: a systematic review. Pancreas. 2018;47(1):12–7.
50. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010;252(2):207–14.
51. Ven Fong Z, Correa-Gallego C, Ferrone CR, Veillette GR, Warshaw AL, Lillemoe KD, et al. Early drain removal—the middle ground between the drain versus no drain debate in patients undergoing pancreaticoduodenectomy: a prospective validation study. Ann Surg. 2015;262(2):378–83.
52. Cheatham ML, Chapman WC, Key SP, Sawyers JL. A meta-analysis of selective versus routine nasogastric decompression after elective laparotomy. Ann Surg. 1995;221(5):469–76; discussion 76–8

Chapter 54
Pancreatoduodenectomy with Portal Vein Resection

Dyre Kleive, Morten Vetrhus, Michael A. Silva, Svein Olav Bratlie, and Kjetil Søreide

Take Home Messages

- Resection of the portomesenteric vein is accepted practice in selected patients
- High-quality cross-sectional, contrast-enhanced CT-imaging is a must for adequate pre-operative planning
- Four types of reconstruction are defined according to the international study group of pancreatic surgery (ISGPS)
- The majority of vein-resections can be managed with simple suture or end-to-end anastomosis
- Numerous alternatives exist for graft types used, with inherent benefits and risks
- Neoadjuvant therapy and response evaluation are likely to aid in proper patient selection

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Pearls and Pitfalls
- Planned resection is preferred over incidental vein resection
- Planning of type of reconstruction and type of graft before surgery is strongly advised
- If not trained in vascular reconstruction, teaming up with a transplant or vascular surgeon for vein reconstruction is recommended to enhance outcomes
- Graft for reconstruction should be harvested and ready before the portal vein is resected
- Several complications may occur in the short-term, particularly bleeding, thrombosis and loss of graft patency

Future Perspectives
- Better understanding of type, dose and duration of thromboprophylaxis is needed
- The use of graft type in relation to benefits and risks remains undecided
- Optimal biological criteria for appropriate patient selection beyond imaging are needed
- The oncological efficacy remains unclear, with need for better studies
- Controlled trials investigating various types of reconstruction technique for either short- or long-term differences are lacking

54.1 Introduction

Most pancreatic resections are done without vein resection, and venous infiltration was previously a relative if not absolute contraindication to surgery. Over the past decades this has changed, the experience with vein resection has increased, with perioperative outcomes reported equal to or in the same range as for pancreatoduodenectomy done without venous resection. Also, a shift in mind-set from resectable/unresectable has been introduced with the "borderline" and "locally advanced" resectable categories and the introduction of neoadjuvant treatment for many patients with these types of tumors. Hence, experience with vein resections has increased and is now accepted as a standard approach for selected patients in most institutions [1]. This chapter will discuss the role of vein resection in pancreatoduodoenectomy and the technical issues concerning this. Other chapters will discuss issues concerning arterial resections and related specific procedures.

54.2 Historical Background

One of the early reports on vein resection during pancreatoduodenectomy was published in 1951 [2]. In the report, the surgeons recognized tumor attachment to the lateral aspect of the superior mesenteric vein intraoperatively and performed a

segmental vein resection with primary end-to-end anastomosis. Although this likely was one of the first of many publications regarding this topic, the authors cover an impressive number of relevant aspects concerning vein resection during pancreatoduodenectomy, several which are still discussed today. These include different reconstruction techniques, the potential benefit of simultaneous superior mesenteric artery clamping, splenic vein preservation or ligation and the use of intraoperative heparin and postoperative anticoagulation.

In the 1970s, Fortner brought further notice to vascular resection during pancreatic surgery [3]. Due to the high morbidity and mortality associated with the procedure, the method was not widely adopted. However, with the advancement in preoperative work-up, surgical technique, postoperative treatment and anesthesia, the last three decades have provided an extensive amount of literature on the topic and pancreatoduodenectomy with vein resection should now be considered standard of care in high-volume centers delivering state-of-the art pancreatic surgery.

54.3 Oncological Considerations

The main principles of surgical resection for pancreatic cancer engaging the portomesenteric vein axis are the same as for a standard pancreatoduodenectomy. The short- and long-term results for patients undergoing pancreatoduodenectomy with vein resection should assume that of a standard resection. Notably, several centers have reported increased morbidity and mortality with more extensive procedures [4, 5]. However, the risk of morbidity and mortality should not outweigh the prospects of an acceptable quality of life and chance for survival after the procedure. Several reviews and meta-analysis have investigated this during the last decade (Table 54.1) with variable findings concerning both short-and long-term outcomes.

Neoadjuvant chemotherapy is increasingly used for borderline and locally advanced disease [6–8]. Neoadjuvant treatment may aid in the selection of patients with an unfavourable tumor biology. Resection should be offered to patients with signs of vein involvement on preoperative imaging given stable disease or remission on subsequent restaging. The data on neoadjuvant chemotherapy are limited by single-center reports [8, 9]. However, a recent randomized controlled trial was terminated due to favourable results for patients with borderline-resectable pancreatic cancer given neoadjuvant therapy compared to upfront surgery [10]. Further randomized trials are underway [7]. A recent meta-analysis found a 63% resection rate for patients with borderline-resectable tumors after neoadjuvant chemotherapy and the estimated median survival for patients resected, was 25.9 months [11]. This is fairly equal to the results of the ESPAC-4 trial [12] evaluating long-term outcomes in selected patients with primary resectable pancreatic cancer completing both surgical and adjuvant systemic therapy.

Consequently, the proposal of administering neoadjuvant chemotherapy for patients with borderline resectable disease, followed by restaging and resection in patients without disease progression [13] seems reasonable. It is important to bear in mind that several different classifications [14] of resectable, borderline and locally advanced pancreatic tumors exist [15] and stringency in the use and reporting on this is warranted (Box 54.1).

Box 54.1 Borderline Resectable Pancreatic Cancer, According to NCCN [13]

- Solid tumor contact with the SMV or PV > 180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction
- Solid tumor contact with the inferior vena cava
- Solid tumor contact with the common hepatic artery without extension to coeliac trunk or hepatic artery bifurcation allowing for safe and complete resection and reconstruction
- Solid tumor contact with the SMA of ≤180°
- Solid tumor contact with variant arterial anatomy
- For tumors in body and tail of the pancreas: Solid tumor contact with the coealiac trunk >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery and thereby permitting a modified Appelby procedure

54.4 Preoperative Work-Up and Imaging

Decisions regarding resectability should involve multidisciplinary consultation at a high-volume center. A dedicated pancreatic CT [16, 17] or MRI with contrast should be present (within 4 weeks) before decision making or, after restaging in case of neoadjuvant therapy. Sub-millimeter axial sections with a dual-phase pancreatic protocol containing images obtained in both the pancreatic and portal venous phase of contrast enhancement is preferable [18].

The pancreatic parenchymal enhancement will produce the optimal visual contrast differences between the enhanced pancreatic parenchyma and the usually hypoattenuating tumor. Also, the peripancreatic arteries are usually well opacified during this phase, allowing for their concomitant evaluation.

In the second portal venous phase acquisition, the portomesenteric venous system is well opacified and potential tumor growth into the superior mesenteric/portal vein can be assessed [19]. The liver is also maximally enhanced during this phase, which improves detection of hepatic metastases [18]. A structured reporting template ensures that all important data from the scan are documented [16, 17]. The degree and extent of tumor-vein contact should be described and reported (Fig. 54.1). There is reason to believe that preoperative awareness of venous and arterial anatomy has an impact on outcomes [20], as incidental (or, accidental/unplanned) vein resections are associated with higher risk of complications [20].

Table 54.1 Overview of outcomes after pancreatic surgery with vein resection

Publication	No. of studies/patients	Morbidity	Mortality	Survival
Siriwardana, BJS, 2006	52 studies 1646 patients with pancreatectomy and vein resection	Median 42% pr. cohort	5.9% perioperative morality	5.8% 5-year survival
Zhou, World J Surg, 2012	19 studies/2247 patients 661 pancreatectomies with vein resection 1586 pancreatectomies without vein resection	No difference for patients with and without vein resection	No difference for patients with and without vein resection	No difference for patients with and without vein resection
Castleberry, Ann Surg Oncol, 2012	3582 patients 281 pancreatoduodenectomies with vein resection 3301 pancreatoduodenectomies without vein resection	Greater risk-adjusted 30-day morbidity for patients undergoing pancreatoduodenectomy with vein resection	Greater risk-adjusted 30-day mortality for patients undergoing pancreatoduodenectomy with vein resection	Not assessed
Yu, EJSO, 2014	22 studies/2890 patients 794 pancreatoduodenectomies with vein resection 2096 pancreatoduodenectomier without vein resection	No difference for patients with and without vein resection	No difference for patients with and without vein resection	No difference for patients with and without vein resection
Giovinazzo, BJS, 2016	27 studies/9006 patients 1587 pancreatectomies with vein resection 7419 pancreatectomies without vein resection	Increased overall complication rate, relaparotomy rate and rate of postpancreatectomy hemorrhage for patients with vein resection	Increased 30-day mortality rate for patients with vein resection	No significant difference in estimated median survival
Beane, HPB, 2017	1414 patients, 197 pancreatoduodenectomies with vein resection	No difference in overall morbidity	No difference in overall mortality	Not assessed
Bell, Surg Oncol, 2017	4145 patients, 1207 patients with pancreatodudoenectomy with vein resection	No difference in postoperative morbidity	Higher postoperative mortality for patients undergoing pancreatodudoenectomy with vein resection	Worse overall 5-year survival for patients undergoing pancreatoduodenectomy with vein resection

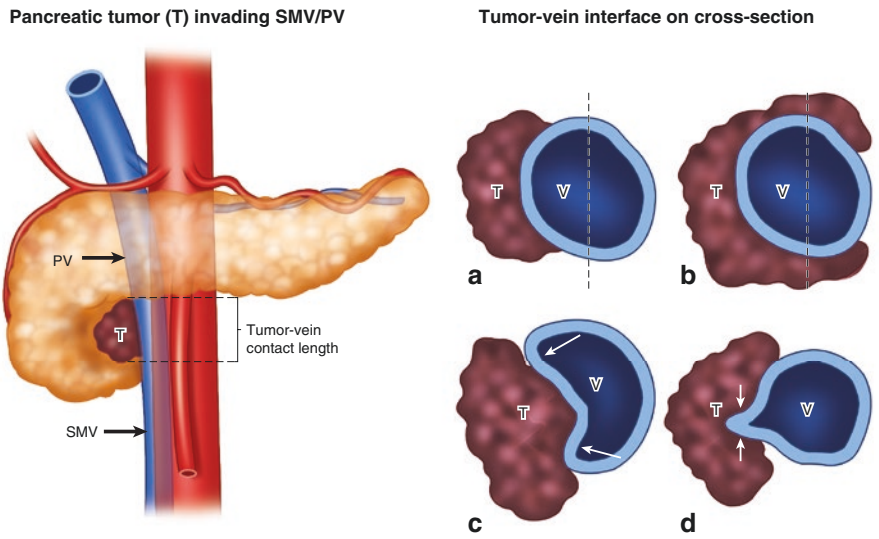

Fig. 54.1 Venous tumor contact in pancreatic cancer invasion of SMV/PV. (**a**) Less than or equal to 180° tumor contact without deformity. (**b**) More than 180° tumor contact without deformity. (**c**) Less than or equal to 180° tumor contact with deformity (arrows). (**d**) Tear drop deformity (arrows). *SMV* superiomesenteric vein, *PV* portal vein, *T* tumor, *V* vein. *Dashed line* 180° of lumen circumference

54.5 Classifications

An initial classification system for venous resections was proposed in 1992 by Ishikawa [21] and several modifications thereof have been presented later. In 2014, the International Study Group of Pancreatic Surgery (ISGPS), proposed a consensus classification of 4 different types of vein resection [14] (Box 54.2).

Box 54.2 Classification of Venous Resections (According to ISGPS)

- Type 1: partial venous excision with direct closure (venorraphy) by suture closure.
- Type 2: partial venous excision using a patch.
- Type 3: segmental resection with primary end-to-end venovenous anastomosis.
- Type 4: segmental resection with interposed venous conduit and at least two anastomoses.

54.6 Types of Venous Reconstruction

With appropriate definitions for common reporting of data, future evidence-based recommendations can be achieved based on a common understanding and comparison between series and trials [14]. The four types of resections are summarized in Fig. 54.2.

The most frequent reported reconstruction technique is end-to-end anastomosis (Type 3) and venorrhaphy (Type 1). In a review of over 2000 vein resections the Type 1 and 3 techniques were used in almost 80% of the cases [22].

Long segments of the SMV/PV have been reported removed and subsequently reconstructed with an end-to-end anastomosis by methods such as the Cattell-Braasch maneuver and liver mobilization [23, 24]. End-to-end anastomosis for involved segments up to 3 cm is considered sufficient by most surgeons, while some consider longer segments (median 4.6 cm, range 3–7 cm of length) doable for an end-to-end anastomosis [23]. However, end-to-end anastomosis after resection of longer

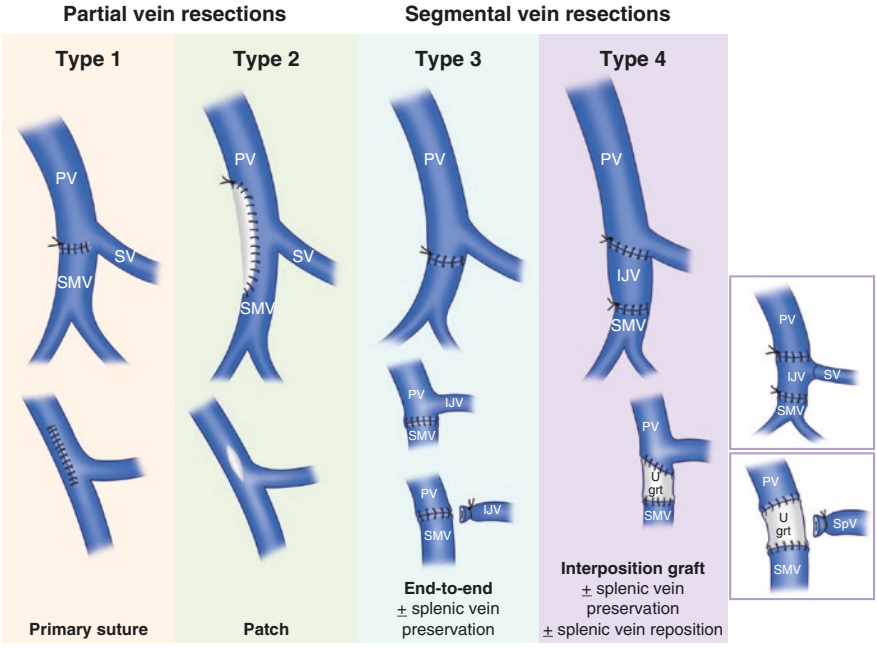

Fig. 54.2 Types of reconstruction techniques. Legend: Type 1 and 2 reconstruction refers to partial vein wall resection and closure either with a venorraphy (Type 1) or a patch (Type 2). Type 3 and 4 resections refers to segmental resections with either primary end-to-end anastomosis (Type 3) or interposition graft (Type 4). Reconstruction can be done with or without reposition of the splenic vein in case of segmental resections. Note the oblique resection of Type 4 to preserve the splenic vein. Several alternatives exist to reconstruction beyond the main described techniques

Table 54.2 Overview of patches and interposition material used

Graft	Description	Pros	Cons
Autograft	Left renal vein Great saphenous vein Gonadal vein Iliac vein	No rejection No infection	Size matching Complications from site of graft harvest Time consuming
Allograft		Ready for use Time efficient No graft harvest needed	Possible graft rejection Stenosis⇑ Legal issues outside the transplant setting in some centers Only in units with Tx
Xenograft		Ready for use Time efficient No graft harvest needed	Graft rejection ⇑ Costs ⇑
Synthetic	PTFE (Teflon) PETE (Dacron)	Ready for use No graft harvest site	Infection risk ⇑ Costs ⇑ Early vein thrombosis risk ⇑
Peritoneal		No rejection No infection	Time consuming Size mismatch

PTFE polytetrafluoroethylene, *PETE* polyethylene terephthalate

segments (>3 cm) have also been reported to have poorer patency rates at longer follow up [25].

54.6.1 Vein Reconstruction with Interposition Graft (Type 4)

A variety of patch or interposition materials have been reported (Table 54.2), ranging from bovine pericardium, synthetic material, peritoneal material, autologous or allo-veins, autologous or allo-arteries [22, 26–34].

The likelihood that an interposition graft will be needed for reconstruction too, should be anticipated in the planning phase before surgery. However, the need for end-to-end anastomosis or interposition graft is likely to relay on surgeon preference. For all types of reconstruction, however, anticoagulation with heparin is usually compulsory, as in other vascular surgical procedures. Some authors recommend heparin before clamping the vein [35], while others do not [1]. Clamping of the superior mesenteric artery can be performed in order to reduce bowel ischemia. Measuring the clamping time of both the superior mesenteric artery and the SMV/PV seems reasonable, however, the time used for reconstruction and its impact on short-term patency and overall complications is unknown. For all types of reconstruction, a tension free anastomosis or venorraphy is warrented. In the case of end-to-end anastomosis or interposition graft, a growth factor should be in place upon ending the suture. Releasing the distal clamp on the portal vein first will allow for thorough expansion of the reconstruction.

When an interposition graft is needed, autologous veins may be the best option as it is generally more readily available than allogenic material and have superior patency rates compared to synthetic material [28]. A vein of commensurate diameter is advisable in order to avoid flow-limiting stenosis. Veins harvested from different locations have been reported used in this setting: the left renal, the internal jugular and the superficial femoral vein [36]. The vein should be harvested and be ready for use before the superior mesenteric vein is transected and the pancreatic specimen removed.

Some liver transplant centers with tissue banking facilities use donor vein grafts when needed [26]. In the absence of this resource, the patient's internal jugular vein or left renal vein offer the best size match. Harvesting the internal jugular vein often mandates the help of a vascular surgeon and the need for preparing another operative field. In comparison, the left renal vein is far more accessible and can be harvested with ease to fulfil this need. In the following, an example of use of the left renal vein as interposition graft will be explained.

54.7 Surgical Technique: Use of Left Renal Vein as Interposition Graft

Use of the left renal vein has been described by several groups for reconstruction [37–39]. It is of importance that the left renal vein is assessed for suitability for use as a graft before surgery. The patient should have acceptable renal function and anatomical considerations on pre-operative imaging must be assessed, like the rare variation of a retro-aortic left renal vein that may preclude its use.

When a portal vein interposition graft is needed, at the time of the Kockerisation of the duodenum this may be continued with the Cattell-Braasch manoeuvre and expose the left renal vein fully (Fig. 54.3a). The renal vein is then isolated with vascular slings ready to be harvested later. At the pancreaticoduodenectomy that follows, after isolation of the portal vein superiorly, dividing the duodenum at D1 and the pancreatic neck and division of the proximal jejunum, the uncinate process and head of the pancreas are mobilized off the SMV and SMA. At this stage it will be apparent if the PV and SMV actually needs resection to achieve tumor clearance. It will also be clear as to how much length of vein will be lost. One should also assess the length of vein to be resected or if the mesentery is too bulky and non-yielding for mobilization to allow for an end-to-end (Type 3) anastomosis. Then, before proceeding with actually dividing the portal vein for removal of specimen, the next step is to proceed to harvest of the left renal vein graft.

The medial aspect of the left renal vein graft is usually taken with a vascular TA stapler flush with the IVC (Fig. 54.3b). At the renal hilum, two stay sutures are placed just beyond the suprarenal and gonadal veins, to prevent retraction of the vein if it slips through the Satinsky vascular clamp, with an adequate cuff of vein to be over sewn (Fig. 54.3b). The vein is then divided and the graft harvested.

Following this it is one of the authors' practice (Mike Silva) to give the patient 2000 U i.v. heparin and then place a vascular clamp to occlude the SMA inflow to the bowel. This prevents mesenteric and bowel engorgement while the resection and reconstruction of the portal vein takes place. A timer is then started and the pancreatoduodenectomy completed with the specimen removed with a segment of vein.

The interposition graft is then sewn in with a continuous suture starting with the superior anastomosis (Fig. 54.4a). A growth factor is left on the suture when tying it off and a heparin saline flush in to the graft with the clamps taken off for a

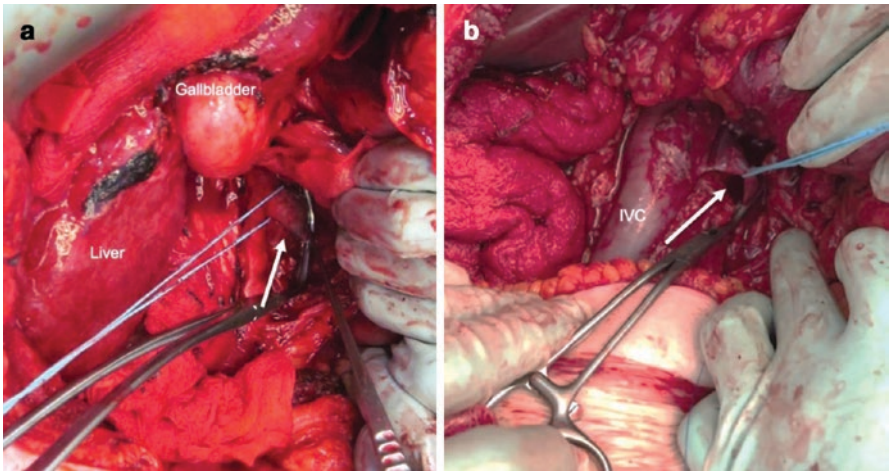

Fig. 54.3 Left renal vein harvest. (**a**) Complete mobilization of the right colon (Catell Brasch maneuver) to identify and isolate the left renal vein (arrow). (**b**) The use of a TA vascular stapler for medial aspect of LRV graft, Satinsky on the lateral part (Images courtesy of Mr. Mike Silva)

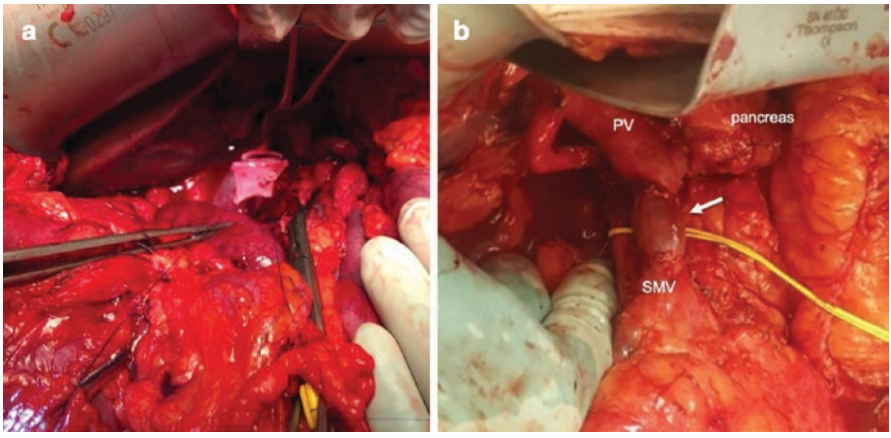

Fig. 54.4 Left renal vein reconstruction. (**a**) interposition graft is sewn in with a continuous suture starting with the superior anastomosis. (**b**) Type 4 reconstruction completed with LRV (arrow)

momentary controlled bleed out to remove any clots that may have formed while the clamps were on, and the reconstruction competed (Fig. 54.4b).

There is no evidence of long-term impact on renal function following the use of a left renal vein graft [40, 41]. However, a slightly higher risk of reversible acute kidney injury during the first 1–3 days has been noted [41].

54.8 Postoperative Treatment and Specific Complications

Post-operative treatment and complications are overall similar to standard pancreatoduodenectomy. In order to identify potential early graft failure or early failure at the reconstructed SMV/PV one could perform an ultrasound scan with Doppler flow of the reconstructed SMV/PV 4-6 hours after the end of the procedure. In the case of early thrombosis or occlusion due to graft kinking, this should lead to reoperation.

54.8.1 Anticoagulation and Extended Post-operative Thromboprophylaxis

Overall, there is considerable heterogeneity in the use of anticoagulation after PV resection and currently no consensus exists on this topic [42–44]. For pancreatic resections, the use of double-dose low-molecular weight heparin for 6 weeks after surgery, increased the number of clinically relevant post-pancreatectomy hemorrhages and need for relaparotomies in an uncontrolled Dutch cohort study [45]. Others have found no difference in the presence of postoperative venous thromboembolism and early portal vein thrombosis between the use of double-dose and single dose low molecular weight heparin [43].

A systematic review [42] compared studies with an anticoagulation policy to no anticoagulation policy after venous resection. They found eight anticoagulation policy studies of a total of 266 patients and five studies reporting no anticoagulation with a total of 95 patients. The anticoagulation policy studies included aspirin, clopidogrel, heparin or warfarin. Only half of patients in the anticoagulation policy group received anticoagulation. There were more prosthetic grafts in the anticoagulation policy group. The overall morbidity and mortality were similar in both groups.

Prevalence and outcome of portomesenteric thrombosis was reported in as many as 27–28% in some series [46, 47] with most occurring late (within a year). Early PV thrombosis is usually reported in 3–7% and highest in patients who received a synthetic graft [42, 47]. Early PV thrombosis was similar between the groups and was associated with a high mortality (40%) [42]. When prosthetic grafts were excluded there was no difference in the incidence of early PV thrombosis between groups.

54.8.2 Left-Sided Portal Hypertension

Sinistral or left-sided portal hypertension has been a matter of debate over the recent years [48–52]. While some argue that it may not be a major clinical issue, as most patients with advanced pancreatic cancer necessitating portal vein resection does not live long enough to experience the relevance of the complications. Failure to reinsert the splenic vein can cause gastric remnant venous congestion, esophageal varices, splenomegaly, or severe or prolonged thrombocytopenia.

In the short-term, no clinically relevant difference is noted between reconstruction or not [50], but risk of varices may increase over the subsequent years [48]. Sacrifice of all potential collateral veins (referred to as the critical veins: left gastric vein, middle colic vein, and superior right colic vein arcade) and absence of any spontaneous splenorenal shunt is associated with risk of formation of varices [52]. Based on the limited data there seems to be a higher risk for sinistral portal hypertension with splenic vein division. Selected reconstruction may be considered, with several techniques reported [49]. Alternative techniques to avoid splenic vein division and need for reinsertion has also been reported [53].

54.9 Clinical and Oncological Outcomes

Use of venous resection has expanded over the years and is increasingly used also in the elderly group of resected patients [54, 55]. Overall, the resection of portomesenteric invasion does not increase survival per se although good outcomes can be achieved [56–59]. The R_0 rate, in the setting of upfront surgery is usually not changed due to growth in the superior mesenteric/portal vein groove [60]. Survival is likely attributed to other biological factors, such as response to chemotherapy, tolerance and number of cycles received and size of tumor. Larger tumor-vein length/interface (Fig. 54.1) is related to bigger tumor-size [59, 61], need for larger vein-resections and associated with both poorer patency rates and overall survival [62–64].

54.10 Conclusions

Portomesenteric vein infiltration by pancreatic and periampullary tumours is considered technically resectable in selected patients. Neoadjuvant chemotherapy is increasingly used to select good surgical candidates. Proper pre-operative evaluation of tumor-vein interface is warranted. Data on patency for different types of reconstruction and different types of graft used is limited. Surgeon preference and familiarity with both vascular surgery and SMV/PV resection is likely to improve both short- and long-term patency at the reconstructive site. Acceptable outcomes both in the short and long-term after pancreatoduodenectomy can be achieved.

References

1. Maley WR, Yeo CJ. Vascular resections during the whipple procedure. Adv Surg. 2017;51(1):41–63. https://doi.org/10.1016/j.yasu.2017.03.004.
2. Moore GE, Sako Y, Thomas LB. Radical pancreatoduodenectomy with resection and reanastomosis of the superior mesenteric vein. Surgery. 1951;30(3):550–3.
3. Fortner JG, Kim DK, Cubilla A, Turnbull A, Pahnke LD, Shils ME. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg. 1977;186(1):42–50.
4. Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T, et al. Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. Br J Surg. 2016;103(12):1683–94. https://doi.org/10.1002/bjs.10221.
5. Kleive D, Sahakyan MA, Berstad AE, Verbeke CS, Gladhaug IP, Edwin B, et al. Trends in indications, complications and outcomes for venous resection during pancreatoduodenectomy. Br J Surg. 2017;104(11):1558–67. https://doi.org/10.1002/bjs.10603.
6. Saharia A, Potter LM, Baio F, Elaileh A, Mobley C, Ghobrial RM, et al. Is surgery-first still a reasonable option in the era of neoadjuvant chemotherapy for resectable pancreatic cancer? Am J Clin Oncol. 2019; https://doi.org/10.1097/coc.0000000000000661.
7. Del Chiaro M, Soreide K. Trials and tribulations of neoadjuvant therapy in pancreatic cancer. Br J Surg. 2018;105(11):1387–9. https://doi.org/10.1002/bjs.11003.
8. Ye M, Zhang Q, Chen Y, Fu Q, Li X, Bai X, et al. Neoadjuvant chemotherapy for primary resectable pancreatic cancer: a systematic review and meta-analysis. HPB (Oxford). 2020; https://doi.org/10.1016/j.hpb.2020.01.001.
9. Araujo RLC, Silva RO, de Padua SC, Milani JM, Huguet F, Rezende AC, et al. Does neoadjuvant therapy for pancreatic head adenocarcinoma increase postoperative morbidity? A systematic review of the literature with meta-analysis. J Surg Oncol. 2020; https://doi.org/10.1002/jso.25851.
10. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268(2):215–22. https://doi.org/10.1097/sla.0000000000002705.
11. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Pancreatology. 2016;16(1):28–37. https://doi.org/10.1016/j.pan.2015.11.007.
12. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24. https://doi.org/10.1016/s0140-6736(16)32409-6.
13. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Pancreatic adenocarcinoma version 1. 2020. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed 2 Feb 2020.
14. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88. https://doi.org/10.1016/j.surg.2014.02.001.
15. Barreto SG, Windsor JA. Justifying vein resection with pancreatoduodenectomy. Lancet Oncol. 2016;17(3):e118–24. https://doi.org/10.1016/s1470-2045(15)00463-5.
16. Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology. 2014;270(1):248–60. https://doi.org/10.1148/radiol.13131184.
17. Brook OR, Brook A, Vollmer CM, Kent TS, Sanchez N, Pedrosa I. Structured reporting of multiphasic CT for pancreatic cancer: potential effect on staging and surgical planning. Radiology. 2015;274(2):464–72. https://doi.org/10.1148/radiol.14140206.
18. Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the soci-

ety of abdominal radiology and the american pancreatic association. Gastroenterology. 2014;146(1):291–304. https://doi.org/10.1053/j.gastro.2013.11.004.
19. Shen YN, Guo CX, Pan Y, Chen YW, Tang TY, Li YW, et al. Preoperative prediction of peripancreatic vein invasion by pancreatic head cancer. Cancer Imaging. 2018;18(1):49. https://doi.org/10.1186/s40644-018-0179-z.
20. Kim PT, Wei AC, Atenafu EG, Cavallucci D, Cleary SP, Moulton CA, et al. Planned versus unplanned portal vein resections during pancreaticoduodenectomy for adenocarcinoma. Br J Surg. 2013;100(10):1349–56. https://doi.org/10.1002/bjs.9222.
21. Ishikawa O, Ohigashi H, Imaoka S, Furukawa H, Sasaki Y, Fujita M, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann Surg. 1992;215(3):231–6. https://doi.org/10.1097/00000658-199203000-00006.
22. Jara M, Malinowski M, Bahra M, Stockmannn M, Schulz A, Pratschke J, et al. Bovine pericardium for portal vein reconstruction in abdominal surgery: a surgical guide and first experiences in a single center. Dig Surg. 2015;32(2):135–41. https://doi.org/10.1159/000370008.
23. Del Chiaro M, Segersvard R, Rangelova E, Coppola A, Scandavini CM, Ansorge C, et al. Cattell-Braasch maneuver combined with artery-first approach for superior mesenteric-portal vein resection during pancreatectomy. J Gastrointest Surg. 2015;19(12):2264–8. https://doi.org/10.1007/s11605-015-2958-1.
24. Zhang J, Qian HG, Leng JH, Cui M, Qiu H, Zhou GQ, et al. Long mesentericoportal vein resection and end-to-end anastomosis without graft in pancreaticoduodenectomy. J Gastrointest Surg. 2009;13(8):1524–8. https://doi.org/10.1007/s11605-008-0777-3.
25. Fujii T, Nakao A, Yamada S, Suenaga M, Hattori M, Takami H, et al. Vein resections >3 cm during pancreatectomy are associated with poor 1-year patency rates. Surgery. 2015;157(4):708–15. https://doi.org/10.1016/j.surg.2014.12.002.
26. Kleive D, Berstad AE, Verbeke CS, Haugvik SP, Gladhaug IP, Line PD, et al. Cold-stored cadaveric venous allograft for superior mesenteric/portal vein reconstruction during pancreatic surgery. HPB. 2016;18(7):615–22. https://doi.org/10.1016/j.hpb.2016.05.010.
27. Meniconi RL, Santoro R, Guglielmo N, Vennarecci G, Lepiane P, Colasanti M, et al. Pancreaticoduodenectomy with venous reconstruction using cold-stored vein allografts: long-term results of a single center experience. J Hepatobiliary Pancreat Sci. 2016;23(1):43–9. https://doi.org/10.1002/jhbp.299.
28. Glebova NO, Hicks CW, Piazza KM, Abularrage CJ, Cameron AM, Schulick RD, et al. Technical risk factors for portal vein reconstruction thrombosis in pancreatic resection. J Vasc Surg. 2015;62(2):424–33. https://doi.org/10.1016/j.jvs.2015.01.061.
29. Dokmak S. Pancreaticoduodenectomy with reconstruction of the mesentericoportal vein by the parietal peritoneum: 'Safi Dokmak vascular graft'. Ann Surg Oncol. 2015;22(Suppl 3):S343–4. https://doi.org/10.1245/s10434-015-4635-8.
30. Lee DY, Mitchell EL, Jones MA, Landry GJ, Liem TK, Sheppard BC, et al. Techniques and results of portal vein/superior mesenteric vein reconstruction using femoral and saphenous vein during pancreaticoduodenectomy. J Vasc Surg. 2010;51(3):662–6. https://doi.org/10.1016/j.jvs.2009.09.025.
31. Chu CK, Farnell MB, Nguyen JH, Stauffer JA, Kooby DA, Sclabas GM, et al. Prosthetic graft reconstruction after portal vein resection in pancreaticoduodenectomy: a multicenter analysis. J Am Coll Surg. 2010;211(3):316–24. https://doi.org/10.1016/j.jamcollsurg.2010.04.005.
32. Yoshioka M, Uchinami H, Watanabe G, Iida M, Nakagawa Y, Miyazawa H, et al. Domino reconstruction of the portal vein using the external iliac vein and an ePTFE graft in pancreatic surgery. J Gastrointest Surg. 2017;21(8):1278–86. https://doi.org/10.1007/s11605-017-3413-2.
33. Shao Y, Yan S, Zhang QY, Shen Y, Zhang M, Wang WL, et al. Autologous falciform ligament graft as a substitute for mesentericoportal vein reconstruction in pancreaticoduodenectomy. Int J Surg. 2018;53:159–62. https://doi.org/10.1016/j.ijsu.2018.03.045.
34. Kleive D, Berstad AE, Sahakyan MA, Verbeke CS, Naper C, Haugvik SP, et al. Portal vein reconstruction using primary anastomosis or venous interposition allograft in pancreatic

surgery. J Vasc Surg Venous Lymphat Disord. 2018;6(1):66–74. https://doi.org/10.1016/j.jvsv.2017.09.003.
35. Tseng JF, Tamm EP, Lee JE, Pisters PW, Evans DB. Venous resection in pancreatic cancer surgery. Best Pract Res Clin Gastroenterol. 2006;20(2):349–64. https://doi.org/10.1016/j.bpg.2005.11.003.
36. Dua MM, Tran TB, Klausner J, Hwa KJ, Poultsides GA, Norton JA, et al. Pancreatectomy with vein reconstruction: technique matters. HPB (Oxford). 2015;17(9):824–31. https://doi.org/10.1111/hpb.12463.
37. Yoshitomi H, Kato A, Shimizu H, Ohtsuka M, Furukawa K, Takayashiki T, et al. Tips and tricks of surgical technique for pancreatic cancer: portal vein resection and reconstruction (with videos). J Hepatobiliary Pancreat Sci. 2014;21(9):E69–74. https://doi.org/10.1002/jhbp.128.
38. Choudry H, Avella D, Garcia L, Han D, Staveley-O'Carroll K, Kimchi E. Use of the left renal vein as a practical conduit in superior mesenteric vein reconstruction. J Surg Res. 2008;146(1):117–20. https://doi.org/10.1016/j.jss.2007.07.022.
39. Choi SH, Hwang HK, Kang CM, Lee WJ. Potential use of left renal vein graft in pancreaticoduodenectomy combined with long segmental resection of the superior mesenteric-splenic-portal vein confluence. JOP. 2011;12(3):234–40.
40. Suzuki T, Yoshidome H, Kimura F, Shimizu H, Ohtsuka M, Kato A, et al. Renal function is well maintained after use of left renal vein graft for vascular reconstruction in hepatobiliary-pancreatic surgery. J Am Coll Surg. 2006;202(1):87–92. https://doi.org/10.1016/j.jamcollsurg.2005.08.001.
41. Loveday BPT, Dib MJ, Sequeira S, Alotaiby N, Visser R, Barbas AS, et al. Renal outcomes following left renal vein harvest for venous reconstruction during pancreas and liver surgery. HPB (Oxford). 2019;21(1):114–20. https://doi.org/10.1016/j.hpb.2018.07.015.
42. Chandrasegaram MD, Eslick GD, Lee W, Brooke-Smith ME, Padbury R, Worthley CS, et al. Anticoagulation policy after venous resection with a pancreatectomy: a systematic review. HPB (Oxford). 2014;16(8):691–8. https://doi.org/10.1111/hpb.12205.
43. Kleive D, Sahakyan M, Soreide K, Brudvik KW, Line PD, Gladhaug IP, et al. Risk for hemorrhage after pancreatoduodenectomy with venous resection. Langenbecks Arch Surg. 2018;403(8):949–57. https://doi.org/10.1007/s00423-018-1721-y.
44. Krepline AN, Christians KK, George B, Ritch PS, Erickson BA, Tolat P, et al. Venous thromboembolism prophylaxis during neoadjuvant therapy for resectable and borderline resectable pancreatic cancer—is it indicated? J Surg Oncol. 2016;114(5):581–6. https://doi.org/10.1002/jso.24361.
45. Hanna-Sawires RG, Groen JV, Klok FA, Tollenaar R, Mesker WE, Swijnenburg RJ, et al. Outcomes following pancreatic surgery using three different thromboprophylaxis regimens. Br J Surg. 2019;106(6):765–73. https://doi.org/10.1002/bjs.11103.
46. Mohammed S, Mendez-Reyes JE, McElhany A, Gonzales-Luna D, Van Buren G, Bland DS, et al. Venous thrombosis following pancreaticoduodenectomy with venous resection. J Surg Res. 2018;228:271–80. https://doi.org/10.1016/j.jss.2018.02.006.
47. Snyder RA, Prakash LR, Nogueras-Gonzalez GM, Kim MP, Aloia TA, Vauthey JN, et al. Vein resection during pancreaticoduodenectomy for pancreatic adenocarcinoma: Patency rates and outcomes associated with thrombosis. J Surg Oncol. 2018;117(8):1648–54. https://doi.org/10.1002/jso.25067.
48. Mizuno S, Kato H, Yamaue H, Fujii T, Satoi S, Saiura A, et al. Left-sided portal hypertension after pancreaticoduodenectomy with resection of the portal vein/superior mesenteric vein confluence in patients with pancreatic cancer: A project study by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. Ann Surg. 2019; https://doi.org/10.1097/sla.0000000000003487.
49. Ono Y, Tanaka M, Matsueda K, Hiratsuka M, Takahashi Y, Mise Y, et al. Techniques for splenic vein reconstruction after pancreaticoduodenectomy with portal vein resection for pancreatic cancer. HPB (Oxford). 2019; https://doi.org/10.1016/j.hpb.2019.01.017.

50. Tanaka H, Nakao A, Oshima K, Iede K, Oshima Y, Kobayashi H, et al. Splenic vein reconstruction is unnecessary in pancreatoduodenectomy combined with resection of the superior mesenteric vein-portal vein confluence according to short-term outcomes. HPB (Oxford). 2017;19(9):785–92. https://doi.org/10.1016/j.hpb.2017.02.438.
51. Yu X, Bai X, Li Q, Gao S, Lou J, Que R, et al. Role of collateral venous circulation in prevention of sinistral portal hypertension after superior mesenteric-portal vein confluence resection during pancreaticoduodenectomy: a single-center experience. J Gastrointest Surg. 2019; https://doi.org/10.1007/s11605-019-04365-z.
52. Tanaka M, Ito H, Ono Y, Matsueda K, Mise Y, Ishizawa T, et al. Impact of portal vein resection with splenic vein reconstruction after pancreatoduodenectomy on sinistral portal hypertension: Who needs reconstruction? Surgery. 2019;165(2):291–7. https://doi.org/10.1016/j.surg.2018.08.025.
53. Chua TC, de Reuver PR, Staerkle RF, Neale ML, Arena J, Mittal A, et al. Transverse closure of mesenterico-portal vein after vein resection in pancreatoduodenectomy. Eur J Surg Oncol. 2016;42(2):211–8. https://doi.org/10.1016/j.ejso.2015.08.167.
54. Fang JZ, Lu CD, Wu SD, Huang J, Zhou J. Portal vein/superior mesenteric vein resection in pancreatic cancer treatment in the elderly. Medicine (Baltimore). 2017;96(27):e7335. https://doi.org/10.1097/md.0000000000007335.
55. Kanda M, Fujii T, Suenaga M, Takami H, Inokawa Y, Yamada S, et al. Pancreatoduodenectomy with portal vein resection is feasible and potentially beneficial for elderly patients with pancreatic cancer. Pancreas. 2014;43(6):951–8. https://doi.org/10.1097/mpa.0000000000000136.
56. Xie ZB, Li J, Gu JC, Jin C, Zou CF, Fu DL. Pancreatoduodenectomy with portal vein resection favors the survival time of patients with pancreatic ductal adenocarcinoma: a propensity score matching analysis. Oncol Lett. 2019;18(5):4563–72. https://doi.org/10.3892/ol.2019.10822.
57. Siriwardana HP, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. Br J Surg. 2006;93(6):662–73. https://doi.org/10.1002/bjs.5368.
58. Ravikumar R, Sabin C, Abu Hilal M, Al-Hilli A, Aroori S, Bond-Smith G, et al. Impact of portal vein infiltration and type of venous reconstruction in surgery for borderline resectable pancreatic cancer. Br J Surg. 2017;104(11):1539–48. https://doi.org/10.1002/bjs.10580.
59. Imamura T, Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, et al. Prognostic role of the length of tumour-vein contact at the portal-superior mesenteric vein in patients having surgery for pancreatic cancer. Br J Surg. 2019;106(12):1649–56. https://doi.org/10.1002/bjs.11328.
60. Kleive D, Labori KJ, Line PD, Gladhaug IP, Verbeke CS. Pancreatoduodenectomy with venous resection for ductal adenocarcinoma rarely achieves complete (R0) resection. HPB (Oxford). 2020;22(1):50–7. https://doi.org/10.1016/j.hpb.2019.05.005.
61. Kurihara C, Yoshimi F, Sasaki K, Nakao K, Lijima T, Kawasaki H, et al. Impact of portal vein invasion and resection length in pancreatoduodenectomy on the survival rate of pancreatic head cancer. Hepato-Gastroenterology. 2013;60(127):1759–65.
62. Tran Cao HS, Balachandran A, Wang H, Nogueras-Gonzalez GM, Bailey CE, Lee JE, et al. Radiographic tumor-vein interface as a predictor of intraoperative, pathologic, and oncologic outcomes in resectable and borderline resectable pancreatic cancer. J Gastrointest Surg. 2014;18(2):269–78.; discussion 78. https://doi.org/10.1007/s11605-013-2374-3.
63. Fujii T, Nakao A, Yamada S, Suenaga M, Hattori M, Takami H, et al. Vein resections >3 cm during pancreatectomy are associated with poor 1-year patency rates. Surgery. 2015;157(4):708–15. https://doi.org/10.1016/j.surg.2014.12.002.
64. Bell R, Ao BT, Ironside N, Bartlett A, Windsor JA, Pandanaboyana S. Meta-analysis and cost effective analysis of portal-superior mesenteric vein resection during pancreatoduodenectomy: impact on margin status and survival. Surg Oncol. 2017;26(1):53–62. https://doi.org/10.1016/j.suronc.2016.12.007.

Chapter 55
The Artery-First Approach in Pancreatic Cancer Surgery

Jeremy J. French and Sanjay Pandanaboyana

Take Home Messages

- There are six artery-first approaches described which provide primary access to different portions of the SMA.
- Each approach has a specific indication depending on the location of the tumour in the pancreas.
- A combination of more than one approach improves access and exposure to the SMA.
- Retrospective studies suggests an artery-first approach may improve peri-operative outcomes, margin status and survival. However, a single RCT comparing artery-first approach with standard pancreatoduodenectomy showed comparable outcomes.

Pearls and Pitfalls

- The principle of an artery-first approach relates mainly to the SMA. However, borderline resectable and locally advanced tumours in the neck of the pancreas with suspicious involvement of common hepatic artery warrant a common hepatic artery first approach to ensure resectability.

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- The various artery-first approaches complement each other with regards to exposure to the SMA at various levels. A combination of approaches may be beneficial in order to expose the length of the SMA particularly in patients post neoadjuvant therapy. Proficiency in more than one approach is recommended.
- A circumferential skeletonisation of the SMA should be avoided when feasible to reduce risk of chyle-leak and postoperative diarrhoea.
- A pancreas protocol CT with an arterial phase is paramount to clearly identify anatomical variations in SMA and common hepatic artery supply particularly post neoadjuvant treatment. The CT scan may not differentiate tumour from post chemotherapy fibrosis but lack of progression on RECIST criteria would warrant a trial dissection using the artery-first approach.

Future Perspectives

- Further RCT's are warranted to explore the benefits of each artery-first approach compared to standard pancreatoduodenectomy to evaluate the perioperative and oncological outcomes.
- An artery-first approach may have an important role in patients receiving neoadjuvant therapy for borderline and locally advanced pancreatic cancer, to differentiate tumour from fibrous tissue along SMA and may further improve R0 resection rates. This needs to explored in future studies
- Further studies are warranted to confirm the feasibility of a laparoscopic/robotic artery-first approach in terms of its safety, perioperative and oncological outcomes.

55.1 Introduction

Pancreatoduodenectomy followed by adjuvant chemotherapy is still considered standard of care for pancreatic head malignancy. In spite of a potentially curative surgery, the rates of R1 resection remain high with the majority of patients developing recurrence either locally or liver metastasis within the first 2 years [1, 2]. The site of a margin positive resection is often along the superior mesenteric artery and is an established adverse prognostic factor for local recurrence [1]. Refinements in the surgical technique to improve R0 resection rates along the superior mesenteric artery (SMA) margin both during pancreatoduodenectomy and distal pancreatectomy have led to the concept and development of artery first approach to pancreatic cancer surgery [3]. The artery-first approach to pancreatoduodenectomy was first described in 1993 by Nakoa et al. [4]. The SMA was approached in the mesentery of the jejunum (mesenteric approach), allowing early division of the inferior pancreatoduodenal artery and dissection along the SMA. This report was followed by several modifications allowing exposure of SMA along its course from the aorta to the small bowel mesentery [5–11].

Earlier identification of tumor along the SMA margin will ensure no irreversible steps such as division of pancreatic neck are undertaken thereby avoiding a margin

positive resection. Furthermore, the increasing use of neoadjuvant therapy for borderline and locally advanced pancreatic cancers has created the added challenge of local staging predominantly along the superior mesenteric artery [11, 12]. An artery-first approach has a potential role allowing trial dissection and frozen sections along the SMA at an earlier stage of pancreatoduodenectomy before irreversible steps are taken to identify tumor regression along this margin.

55.2 Technical Descriptions of *Open* Artery First Approaches to Pancreatic Head Cancer

There are six different techniques of artery first approach previously described in the literature [3]. Each approach provides exposure to the SMA from its origin from the aorta through the pancreas and as it enters into the bowel mesentery (Fig. 55.1).

A brief description of the individual approach and advantages and disadvantages with each approach are summarized below.

55.2.1 Posterior Approach

The posterior approach is indicated for tumours in the head and neck of the pancreas with involvement of Portal-superior mesenteric vein. It may not be feasible in patients with peripancreatic inflammation and adhesions around the head of the

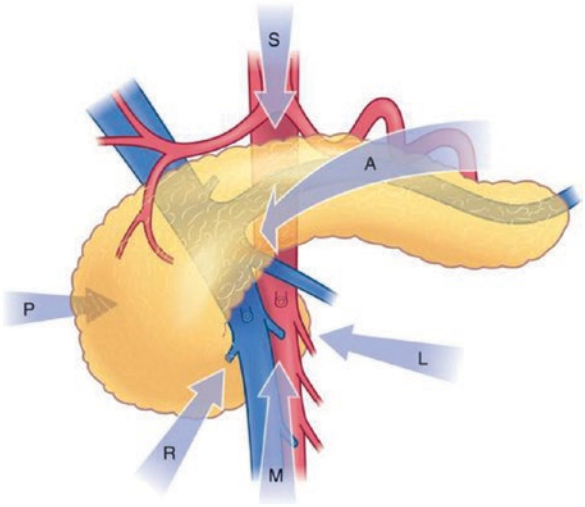

Fig. 55.1 Diagram showing the six approaches to the superior mesenteric artery. *S* superior approach, *A* anterior approach, *P* posterior approach, *L* left posterior approach, *R* right/medial uncinate approach, *M* mesenteric approach. (Reproduced from *British Journal of Surgery* 2018 May;105(6):628–636. With permission from John Wiley and Sons)

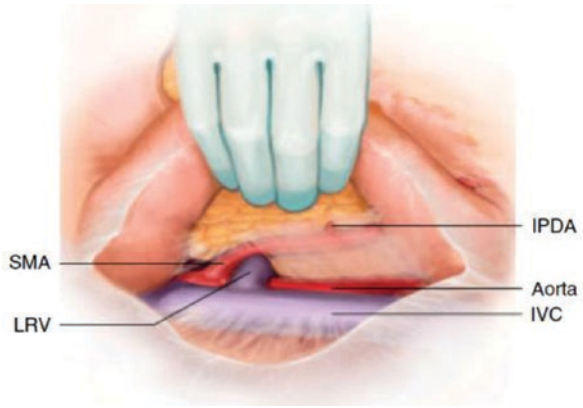

Fig. 55.2 Posterior approach, exposing the origin of superior mesenteric artery (SMA) in front of the left renal vein after Kocherization. For clarity the SMA has been made more apparent. *IPDA* inferior pancreatoduodenal artery, *LRV* left renal vein, *IVC* inferior vena cava. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from John Wiley and Sons)

pancreas. However, given the relative familiarity with extended kocherisation and exposure of the retroperitoneum by most hepatobiliary surgeons, this is the most commonly used artery-first approach.

The posterior approach is the most frequently used approach amongst the artery first approaches during open pancreatoduodenectomy [5, 6]. The dissection begins with extended kocherisation of the duodenum, exposing the left renal vein, inferior vena cava and the anterior surface of aorta. The SMA is then exposed in front the left renal vein (Fig. 55.2). A sharp dissection is undertaken to expose the adventitia of the SMA by dividing the perivascular connective tissue. This plane is then maintained along the SMA and dissection continued towards the head of the pancreas to where it crosses the duodenum. The origins of the superior and inferior pancreatoduodenal arteries can be identified and ligated as they enter the pancreatic head and uncinate process respectively.

55.2.2 Medial Uncinate Approach

The medial uncinate approach is indicated for tumours of the uncinate process of the pancreas [7, 8]. This approach will allow early identification of SMA involvement for tumour in this location before any irreversible steps such as division of neck of the pancreas are undertaken.

Similar to the posterior approach, an extended kocherisation is undertaken first. A further Cattell-Braasch manoeuvre is then undertaken which will allow the right colon and small bowel to be retracted well to the left facilitating the exposure of superior mesenteric vein as it passes over the third part of the duodenum. A further division of the ligament of Treitz can be undertaken and translocation of the proximal jejunum with its intact mesentery into the supracolic compartment. This allows alignment of the uncinate process with the jejunal mesentery and further exposure

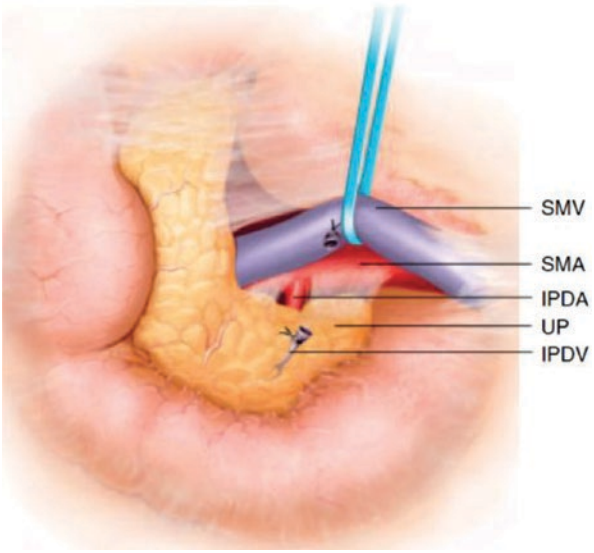

Fig. 55.3 Medial uncinate approach. Demonstrating the uncinate process (UP), inferior pancreatoduodenal artery (IPDA) and vein (IPDV), superior mesenteric artery (SMA) and vein (SMV) after kocherization and mobilization of the duodenojejunal flexure. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from John Wiley and Sons)

of superior mesenteric vein in the first instance. The superior mesenteric vein is then dissected from the pancreas often requiring division of small venous tributaries and thereby exposes the SMA (Fig. 55.3). A sharp dissection is undertaken to expose the adventitia of the SMA by dividing the perivascular connective tissue. The dissection on the SMA is then carried out under the neck of the pancreas towards its origin from the aorta. The inferior pancreatoduodenal artery is encountered on the way and is ligated and divided at its origin.

The perceived draw-back of the uncinate approach is a late identification of a replaced right hepatic artery, however this can be addressed by starting the posterior approach first until the replaced right hepatic artery is identified and then undertaking the uncinate approach and join the 2 planes of dissection.

55.2.3 Left Posterior Approach

The left posterior approach allows exposure of the SMA without mobilisation of the duodenum or colon and is indicated for tumours of the posterior aspect of the head of the pancreas and the uncinate process [9].

Before any dissection is undertaken, the proximal jejunum is pulled to the left and the first and second jejunal arteries are divided. Further traction on the proximal jejunum produces a counter clockwise rotation to the SMA that allows identification and division of the inferior pancreatoduodenal artery, arising from the posterior surface of the SMA. This will allow the SMA to be free and retreated to the right with

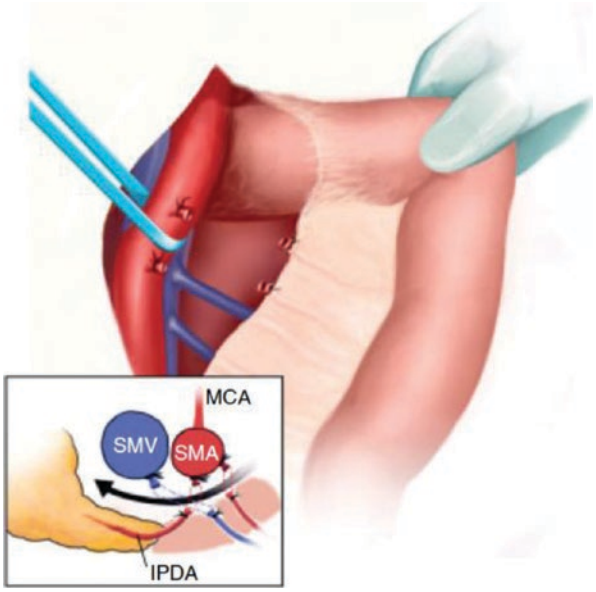

Fig. 55.4 Left posterior approach. Exposing the first and second jejunal arteries at their origin on the superior mesenteric artery (SMA) in the transverse mesocolon. Further traction on the proximal jejunum produces a counter clockwise rotation to the SMA that allows identification and division of the inferior pancreatoduodenal artery (IPDA) arising from the posterior surface of the SMA (inset). *MCA* middle colic artery, *SMV* superior mesenteric vein. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from John Wiley and Sons)

exposure of the SMV under the SMA (Fig. 55.4). The first jejunal branch of the SMV is divided and the superior mesenteric vein is skeletonized up to its confluence with the splenic vein. This frees the superior mesenteric vein and SMA from the uncinate process and the mesentery of the proximal jejunum. The proximal jejunum is then divided and the further part of the duodenum is transposed into the supracolic compartment. Further dissection from here on is similar to the uncinate first approach.

55.2.4 Inferior Infracolic Approach (Mesenteric Approach)

This approach allows exposure of SMA at the base of transverse mesocolon and is indicated for tumours from the ventral pancreas with suspicion of infiltration of SMA [10].

The duodeno-jejunal flexure is mobilized first. The inferior mesenteric vein is encountered during the mobilization and is divided. The SMA is then palpated at the base of transverse mesocolon and the peritoneum overlying it is divided (Fig. 55.5). The SMA and the superior mesenteric vein to its right are exposed. The middle colic artery is identified arising from the SMA and can be divided at its origin from the

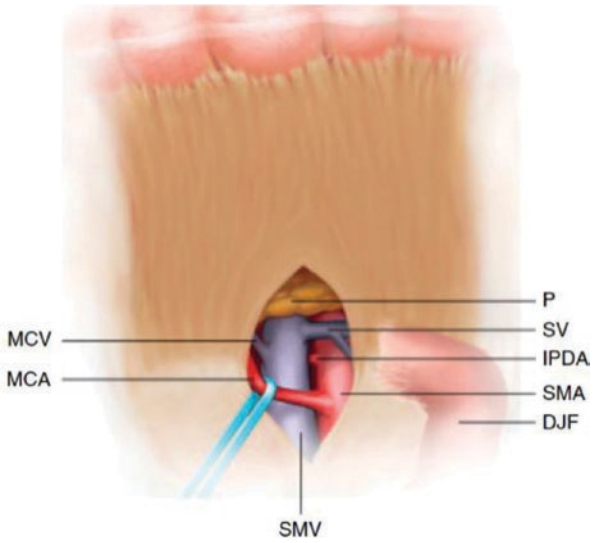

Fig. 55.5 Inferior infracolic approach (mesenteric approach). Exposing the superior mesenteric artery (SMA) and vein (SMV) and branches after dividing the peritoneum to the right of the duodenojejunal flexure (DJF) in the transverse mesocolon. *P* pancreas, *SV* splenic vein, *MCV* middle colic vein, *IPDA* inferior pancreatoduodenal artery, *MCA* middle colic artery. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from John Wiley and Sons)

SMA to allow a wide opening at the base of transverse colon for wider exposure. The dissection on the SMA is carried towards the dorsal surface of the pancreas and this allows exposure of the inferior pancreatoduodenal artery at its origin, often arising from the first jejunal artery. After division dissection on the SMA is continued along the anterior and medial aspects of it towards the neck of the pancreas. Several small venous tributaries from the superior mesenteric vein are encountered during the dissection and divided allowing complete mobilization of superior mesenteric vein during the process.

The added advantage of this approach is earlier identification of SMA involvement without the need for kocherisation of the duodenum with minimal handling of the head of the pancreas allowing the so called "no-touch" pancreatoduodenectomy and thereby prevents tumor cell dissemination [11]. This approach is particularly popular amongst Japanese surgeons.

55.2.5 Inferior Supracolic Approach (Anterior Approach)

This approach is advocated for tumours along the inferior border of the pancreas [11]. Unlike the Inferior infracolic approach, the original description described division of the antrum of the stomach and neck of the pancreas to expose the superior

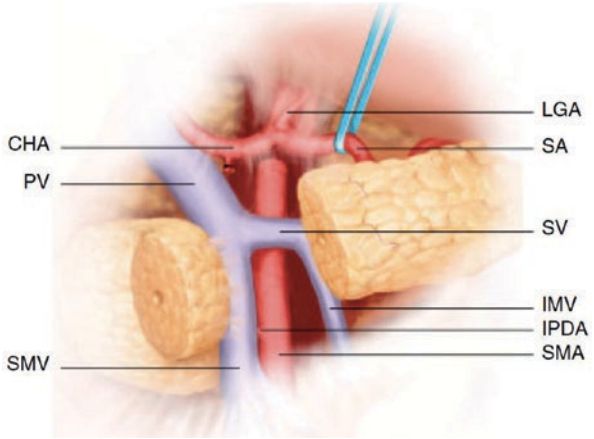

Fig. 55.6 Inferior supracolic approach (anterior approach). Demonstrating the superior mesenteric artery (SMA) and vein (SMV), splenic vein (SV) and coeliac axis and its branches after division of the neck of the pancreas. *LGA* left gastric artery, *CHA* common hepatic artery, *SA* splenic artery, *PV* portal vein, *IMV* inferior mesenteric vein, *IPDA* inferior pancreatoduodenal artery. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from Wiley)

mesenteric vein and SMA (Fig. 55.6). It is however possible to expose the superior mesenteric vein and SMA along the inferior edge of the pancreas to determine resectability before division of the neck of the pancreas. This approach also entails a reverse kocherisation, i.e. the mobilisation of the pancreas head is left until the dissection of the SMA and SMV is completed. Then an *enbloc* mobilisation of the duodenum and pancreas head undertaken in a plane posterior to the Gerotas fascia and anterior the left renal vein and inferior vena cava.

55.2.6 Superior Approach

The superior approach is indicated for tumours arising from the dorsal surface of the pancreas with suspicious common hepatic artery involvement. The common hepatic artery is exposed first in the lesser sac and dissection carried right to left towards the coeliac axis exposing the origins of the gastroduodenal artery, splenic artery and the left gastric artery (Fig. 55.7). The lymph nodes anterior to the common hepatic artery are removed. Once the origin of the coeliac axis is exposed, a caudal retraction of the pancreas is undertaken to facilitate exposure of the SMA. The exposure of SMA through the superior approach can be challenging in patients with a low origin of SMA and one of the other approaches will be more suitable depending on the location of the tumor. There are no published studies describing the outcomes of a superior artery-first approach.

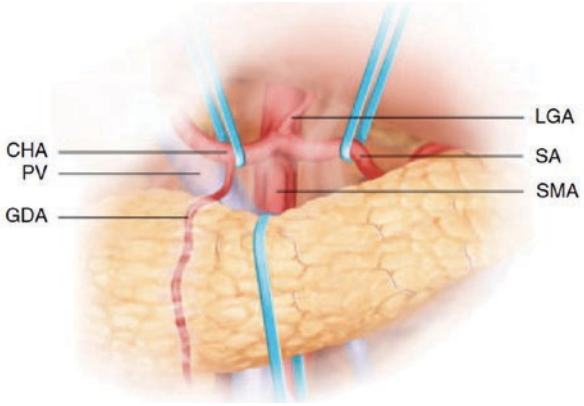

Fig. 55.7 Superior approach. Demonstrating the axis and its branches and the superior mesenteric artery (SMA) in the lesser sac above the neck of the pancreas. *LGA* left gastric artery, *CHA* common hepatic artery, *SA* splenic artery, *PV* portal vein, *GDA* gastroduodenal artery. (Reproduced from *British Journal of Surgery* 2012;99:1027–1035. With permission from Wiley)

55.3 Technical Descriptions of Laparoscopic Artery-First Approaches to Pancreatic Head Cancer

The feasibility of a laparoscopic artery-first approach was explored in few studies in the recent past. Nagakawa et al. first described the laparoscopic uncinate first pancreatoduodenectomy approach in 2015 [13]. After an initial kocherisation and mobilisation of the duodeno-jejunal flexure, proximal jejunum was divided and translocated into the supracolic compartment. This brings the duodeno-jejunal flexure in line with the uncinate process of the pancreas. Similar to the open uncinate first approach, the left posterior side of the SMA and superior mesenteric vein are exposed first. Dissection along SMA exposes the branches of the inferior pancreatoduodenal artery and these are divided at positions where they enter and exit the uncinate process before dissecting the pancreatic head from the right aspect of the SMA completing the dissection along the SMA towards its origin from the aorta. Ten patients who underwent a laparoscopic artery-first approach were compared with 22 patients undergoing conventional laparoscopic pancreatoduodenectomy. There was no significant difference in the operating times between the two groups. However, the intraoperative blood loss was significantly lower in the uncinate first approach when compared to the conventional laparoscopic pancreatoduodenectomy group (162.7 mL vs. 463.8 mL, respectively; P = 0.023).

Chen et al. [14] similarly compared the laparoscopic uncinate first approach and open uncinate first approach in a series of 102 patients. Although the mean operation time was significantly longer in the laparoscopic pancreatoduodenectomy group, laparoscopic artery-first group was associated with lower intraoperative

blood loss, shorter first flatus time, shorter diet start time and lower hospital stay. The rates of overall postoperative complications and postoperative fistula rates were comparable between both groups. The postoperative oncological outcomes were again comparable between both groups. Pedziwiatr et al. [15] compared the 12 laparoscopic uncinate first approaches with 19 patients who underwent a classical laparoscopic pancreatoduodenectomy specifically looking at oncological outcomes. The lymph node yield was higher in the laparoscopic artery-first group (19 vs. 13), with comparable R0 resection rates along the SMA margin and other postoperative outcomes.

In our experience, predominantly with the robotic approach, the dissection of SMA and superior mesenteric vein along the uncinate process is greatly augmented with the 3D view which facilitates accurate dissection along the adventitia of the SMA. Furthermore, the robotic approach has the added advantage of facilitating endosuturing with relative ease compared to a laparoscopic approach for any bleeding encountered from small venous tributaries along the SMA. Further improvements however are needed with the energy devices currently available with the robotic platforms. The long learning curve of robotic pancreatoduodenectomy (80 procedures) to achieve proficiency means the likelihood of trial comparing a standard open pancreatoduodenectomy with robotic artery-first approach is unlikely in the near future. However as more centers undertake robotic pancreatoduodenectomy, we may be able to explore the benefits of artery-first approach outside a trial setting.

55.4 Evidence from Systematic Reviews and Metaanalysis

Three systematic reviews [16–18] have summarized the available evidence regarding the perceived benefits of artery-first approach with standard pancreatoduodenectomy. A metaanalysis [16] of 14 studies compared artery-first pancreatoduodenectomy with standard pancreatoduodenectomy. Artery-first pancreatoduodenectomy was associated with less intraoperative bleeding, fewer blood transfusions and higher rates of portal vein resections. In addition the risk of post-operative pancreatic fistula and delayed gastric emptying was lower in the artery-first group. The oncological outcomes however were comparable between the 2 groups.

A further metaanalysis [17] including 18 retrospective studies and 1 randomised controlled trial, comparing 771 patients who underwent artery-first approach with 701 patients who underwent a standard pancreatoduodenectomy. The posterior approach was the most frequently used approach. None of the included patients had borderline resectable or locally advanced tumours. Similar to the previous metaanalysis, intraoperative blood loss (mean difference − 389 mL; $P < 0.001$), proportion of patients requiring intraoperative transfusion, pancreatic fistula rates were significantly lower in the artery-first group. The oncological outcomes including the R0 resection rates (75.8% vs. 67%) and overall survival were significantly higher in the artery-first group. Jiang et al. in a further metaanalysis in 2020 including the same studies showed similar outcomes [18].

The data from retrospective studies and systematic reviews stemming from those studies should be interpreted with caution. Firstly, due to the inherent risk of bias and heterogeneity due to non-randomised design. Secondly, it is possible that early detection of patients with positive SMA margin led surgeons to abandon the resection thereby spuriously improving survival outcomes.

55.5 Evidence from Randomised Controlled Trials

Two randomised controlled trials explored the benefits of an artery-first approach. Galle et al. [19] compared 6 patients undergoing standard pancreatoduodenectomy with 6 patients undergoing artery first pancreatoduodenectomy with a *no touch technique* with the primary outcome being the presence of circulating tumor cells in the portal circulation. Prior to resection of the pancreatic head, there was no difference in the number of circulating tumor cells between the 2 groups (range, 0–4 in the standard pancreatoduodenectomy group vs. 1–6 in the artery-first group; P = 0.31). Following resection, an increase in the number of circulating tumor cells was seen in 5 of 6 patients (83%) in the standard pancreatoduodenectomy group but 0 of 6 patients in the artery-first group (P = 0.003). This trial was not powered to evaluate the postoperative and oncological outcomes between the 2 groups.

Sabater et al. [20] recently published the first adequately powered RCT comparing artery-first pancreatoduodenectomy with standard pancreatoduodenectomy. The posterior artery-approach was the preferred artery-first approach. The primary outcome measures were R0 resection, morbidity and mortality. Seventy five patients with periampullary and pancreatic malignant tumours undergoing standard pancreatoduodenectomy were compared with 78 patients undergoing artery-first approach. The R0 resection rates were 77.3% with standard pancreatoduodenectomy and 67.9% with artery-first group, P = 0.194. There were no significant differences in postoperative complication rates and perioperative mortality. The perceived benefits shown in previous retrospective studies and metaanalysis with regards to blood loss, transfusion requirements, postoperative pancreatic fistula and survival advantage could not be demonstrated in the trial.

One of the limitations of the trial was 46% of included patients were those with periampullary malignancy who would generally have a higher R1 resection rate than pancreatic ductal adenocarcinoma and therefore combining both pathologies would make interpretation of resection status difficult. The trial did not explore the long term survival outcomes. Furthermore only one artery first-approach (posterior approach) was used for all pancreatic malignancies, while the published evidence suggests the approach used should depend on the location of the pancreatic tumor in relation to the SMA. A further randomised controlled trial (MAPLE-PD) comparing the mesenteric approach versus conventional approach for pancreatic adenocarcinoma in currently underway in Japan [21]. Further trials are needed to explore the benefits of individual artery-first approaches and perhaps even comparing the various artery-first approaches.

55.6 Evolving Concept of the Artery-First Approach

The technique of laparoscopic artery-first is still evolving and is not fully standardized. The current evidence suggests that a laparoscopic artery-first approach is feasible and the uncinate first approach is the preferred approach. A laparoscopic approach may be associated with improved perioperative outcomes when compared to an open approach. However it is important to acknowledge that although laparoscopic pancreatoduodenectomy is being increasingly undertaken, the evidence from randomised controlled trials regarding the benefits of laparoscopic pancreatoduodenectomy is conflicting [22, 23]. Further trials investigating the safety and oncological benefits of laparoscopic pancreatoduodenectomy are warranted before exploring the benefits of a laparoscopic artery-first approach.

It is important to acknowledge that the enthusiasm to undertake the artery-first approach has risen from the necessity to identify SMA involvement at an earlier stage during dissection and improve the SMA margin, predominantly in patients undergoing surgery first followed by adjuvant chemotherapy. In spite of this, recent evidence suggests only a marginal improvement in R0 resection status with artery-first approach [20] even with aggressive hemi-circumferential nerve plexus dissection [24]. Two thirds of recurrences occur at distant sites after pancreatoduodectomy, suggesting that most patients with pancreatic ducal adenocarcinoma have systemic disease [1]. An aggressive surgery alone may not improve margin status. Two recent trials [25, 26] exploring the benefits of neoadjuvant chemotherapy in resectable and borderline resectable pancreatic cancer have shown improved R0 resection rates in patients receiving neoadjuvant chemotherapy. A standard pancreato-duodenectomy was used in both trials. Perhaps the use of an artery-first approach in these groups of patients receiving neoadjuvant therapy may further improve R0 resection rates and needs to be explored in future trials. The other group of patients who would benefit with an artery-first approach are those undergoing surgical exploration for locally advanced pancreatic cancer after neoadjuvant therapy. It is often difficult to differentiate tumor from fibrous tissue around SMA and artery first approach and frozen sections along the SMA margin may prevent a margin positive resection.

55.7 Conclusion

Since its initial description, the techniques of artery-first pancreatoduodenectomy have evolved. The perceived advantages of artery-first approaches shown in non-randomised studies have not been confirmed in the single randomised controlled trial and the evidence to support routine use of an artery-first approach is lacking. Artery-first pancreatoduodenectomy may still have a role in patients receiving neoadjuvant therapy and this need to be explored in future trials.

References

1. Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, Weiss MJ, Zheng L, Wolfgang CL, He J. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg. 2018;267(5):936–45.
2. Tanaka M, Mihaljevic AL, Probst P, Heckler M, Klaiber U, Heger U, Büchler MW, Hackert T. Meta-analysis of recurrence pattern after resection for pancreatic cancer. Br J Surg. 2019;106(12):1590–601.
3. Sanjay P, Takaori K, Govil S, Shrikhande SV, Windsor JA. 'Artery-first' approaches to pancreatoduodenectomy. Br J Surg. 2012;99(8):1027–35.
4. Nakao A, Takagi H. Isolated pancreatectomy for pancreatic head carcinoma using catheter bypass of the portal vein. Hepato-Gastroenterology. 1993;40:426–9.
5. Pessaux P, Varma D, Arnaud J. Pancreatoduodenectomy: superior mesenteric artery first approach. J Gastrointest Surg. 2006;10:607–11.
6. Vallance A, Young A, Pandanaboyana S, Lodge JP, Smith AM. Posterior superior mesenteric artery first dissection versus classical approach in pancreaticoduodenectomy: outcomes of a case-matched study. Pancreas. 2017;46:276–81.
7. Hackert T, Werner J, Weitz J, Schmidt J, Büchler MW. Uncinate process first—a novel approach for pancreatic head resection. Langenbeck's Arch Surg. 2010;395:1161–4.
8. Shukla PJ, Barreto G, Pandey D, Kanitkar G, Nadkarni MS, Neve R, et al. Modification in the technique of pancreaticoduodenectomy: supracolic division of jejunum to facilitate uncinate process dissection. Hepato-Gastroenterology. 2007;54:1728–30.
9. Kurosaki I, Minagawa M, Takano K, Takizawa K, Hatakeyama K. Left posterior approach to the superior mesenteric vascular pedicle in pancreaticoduodenectomy for cancer of the pancreatic head. JOP. 2011;12:220–9.
10. Weitz J, Rahbari N, Koch M, Büchler MW. The artery first approach for resection of pancreatic head cancer. J Am Coll Surg. 2010;210:e1–4.
11. Hirota M, Kanemitsu K, Takamori H, Chikamoto A, Tanaka H, Sugita H, et al. Pancreatoduodenectomy using a no-touch isolation technique. Am J Surg. 2010;199:e65–8.
12. Barreto SG, Loveday B, Windsor JA, Pandanaboyana S. Detecting tumour response and predicting resectability after neoadjuvant therapy for borderline resectable and locally advanced pancreatic cancer. ANZ J Surg. 2019;89(5):481–7.
13. Nagakawa Y, Hosokawa Y, Sahara Y, Takishita C, Nakajima T, Hijikata Y, Tago T, Kasuya K, Tsuchida A. A novel "artery first" approach allowing safe resection in laparoscopic pancreaticoduodenectomy: the uncinate process first approach. Hepato-Gastroenterology. 2015;62:1037–40.
14. Chen XM, Sun DL, Zhang Y. Laparoscopic versus open pancreaticoduodenectomy combined with uncinated process approach: a comparative study evaluating perioperative outcomes (retrospective cohort study). Int J Surg. 2018;51:170–3.
15. Pędziwiatr M, Pisarska M, Małczak P, Major P, Wierdak M, Radkowiak D, Kulawik J, Dembiński M, Budzyński A. Laparoscopic uncinate process first pancreatoduodenectomy-feasibility study of a modified 'artery first' approach to pancreatic head cancer. Langenbeck's Arch Surg. 2017;402(6):917–23.
16. Negoi I, Hostiuc S, Runcanu A, Negoi RI, Beuran M. Superior mesenteric artery first approach versus standard pancreaticoduodenectomy: a systematic review and meta-analysis. Hepatobiliary Pancreat Dis Int. 2017;16(2):127–38.
17. Ironside N, Barreto SG, Loveday B, Shrikhande SV, Windsor JA, Pandanaboyana S. Meta-analysis of an artery-first approach versus standard pancreatoduodenectomy on perioperative outcomes and survival. Br J Surg. 2018;105(6):628–36.
18. Jiang X, Yu Z, Ma Z, Deng H, Ren W, Shi W, Jiao Z. Superior mesenteric artery first approach can improve the clinical outcomes of pancreaticoduodenectomy: A meta-analysis. Int J Surg. 2020;73:14–24.

19. Gall T, Jacob J, Frampton A, Krell J. Reduced dissemination of circulating tumor cells with no-touch isolation surgical technique in patients with pancreatic cancer. JAMA Surg. 2014;149:482–5.
20. Sabater L, Cugat E, Serrablo A, Suarez-Artacho G, Diez-Valladares L, Santoyo-Santoyo J, et al. Does the artery-first approach improve the rate of R0 resection in Pancreatoduodenectomy?: a multicenter, randomized, controlled trial. Ann Surg. 2019;270(5):738–46.
21. Hirono S, Kawai M, Okada KI, et al. MAPLE-PD trial (Mesenteric Approach vs. Conventional Approach for pancreatic cancer during pancreaticoduodenectomy): study protocol for a multicenter randomized controlled trial of 354 patients with pancreatic ductal adenocarcinoma. Trials. 2018;19:613.
22. Nickel F, Haney CM, Kowalewski KF, Probst P, Limen EF, Kalkum E, Diener MK, Strobel O, Müller-Stich BP, Hackert T. Laparoscopic versus open pancreaticoduodenectomy: a systematic review and meta-analysis of randomized controlled trials. Ann Surg. 2019;271:54–66, [Epub ahead of print]. https://doi.org/10.1097/SLA.0000000000003309.
23. van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet. 2019;4(3):199–207.
24. Inoue Y, Saiura A, Oba A, Kawakatsu S, Ono Y, Sato T, Mise Y, Ishizawa T, Takahashi Y, Ito H. Optimal extent of superior mesenteric artery dissection during pancreaticoduodenectomy for pancreatic cancer: balancing surgical and oncological safety. J Gastrointest Surg. 2019;23(7):1373–83.
25. Jang JY, Han Y, Lee H, Kim SW, Kwon W, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268(2):215–22.
26. Versteijne E, van Eijck CH, Punt CJ, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. Trials. 2016;17(1):127. Published 2016 Mar 9. https://doi.org/10.1186/s13063-016-1262-z.

Chapter 56
Pancreatic Surgery with Arterial Resections

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Take Home Messages

- Traditional resectability criteria are currently challenged by the development of new and more powerful systemic treatments.
- Better systemic control of PDAC, mostly related to the introduction of new multi-agent chemotherapies, allow selected patients to undergo more aggressive surgery.
- Pancreatectomies with arterial resection have similar outcomes compared to "conventional pancreatectomies" in selected groups of patients.

Pearls and Pitfalls

- Rates of mortality and morbidity of pancreatectomies with arterial resection have reached acceptable ranges in the current series.

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- With the emergence of effective neo-adjuvant systemic treatment, selected patients can experience improved long-term survival after undergoing pancreatectomy with arterial resection.
- The experience of this kind of resection is limited in a few institutions.
- The selection of the candidates for pancreatectomy with arterial resection and expertise of the institutions in this operation are important factors influencing the outcome.

Future Perspectives

- More objective and prognostic-based criteria for resection of PDAC need to be defined by the International Scientific Community.
- Larger studies should validate the encouraging results reported by recent publications.
- The indications and techniques for pancreatectomy with artery resection should be standardized.
- Eligibility criteria should be defined by centers where pancreatectomy with artery resection will take place. Volume of cases alone cannot justify the expertise of the center required for pancreatectomy with artery resection.

56.1 Historical Notes and Background

Complete resection is considered as a cornerstone in curative therapy for pancreatic ductal adenocarcinoma cancer (PDAC), nonetheless curative resection for patients with locally advanced disease remains challenging due to the tumor's proximity to peri-pancreatic arteries (hepatic artery, celiac trunk, superior mesenteric artery) and veins (superior mesenteric vein, portal vein) that must be preserved. In 1973, in an effort to surgically treat patients with locally advanced pancreatic cancer without distant metastasis, JG Fortner published a cohort of patients from the Memorial Sloan Kettering Cancer Center who were treated with pancreatectomy that involved large peri-pancreatic vessel resection and reconstruction (regional pancreatectomy) [1]. Dr. Fortner's "regional pancreatectomy" was not widely accepted due to the rate of morbidity and mortality associated to this procedure [2], even though the post-operative mortality rate of "conventional pancreatic resections" was 15 to 20%, which was similar to that of "regional pancreatectomy" during that time period [3–5]. Poor long-term survival result of "regional pancreatectomy" was also often criticized, as patients who underwent "regional pancreatectomy" had a 12-month overall survival rate of 62%. The median survival period after pancreaticoduodenectomy in treating PDAC was 10 months, which was similar to that of palliative surgery [6]. The proceeding guidelines

failed to incorporate arterial resection in treating PDAC involving the peri-pancreatic arteries due to the influence of strong criticism against Fortner's idea on implementing radical artery resection.

Before 2000, pancreatectomy with vascular resection and reconstruction was not commonly performed. Recent reports have shown that PDAC patients who underwent pancreatectomy with vein resection/reconstruction have similar morbidity, mortality and survival rate as those who underwent surgical treatment of tumors that did not involve the veins [7–9]. For this reason, pancreatectomy with vein resection and reconstruction has become the gold standard of achieving curative resection when superior mesenteric vein/portal vein is involved, according to multiple guidelines [10]. In contrast with the wide acceptance of vein resection in treating PDAC, performing pancreatectomy with peri-pancreatic artery resection remains debatable, since there are only few publications that show favorable long-term survival results. These reports are recent studies from specialized centers that show promising long-term survival results associated with pancreatectomy with arterial resection.

This chapter examines the current technical aspects of arterial resection in treating PDAC, delving into the topics of resection and reconstruction of various peripancreatic vasculatures. Recent survival outcomes of patients, who underwent pancreatectomy with arterial resection after the administration of modern systemic therapies, are then depicted.

56.2 Technical Aspects

56.2.1 Cattell-Braasch Maneuver

In order to mobilized the ascending colon, right colonic flexure, and the cecum, surgeons can perform a Kocher maneuver and a Cattel-Braasch maneuver, which is previously executed as a method to rapidly access the retroperitoneal structures in a setting of a trauma event. The root of the small intestine could also be mobilized by following an avascular plane from the retroperitoneum together with the ligament of Treitz (Fig. 56.1a). Following this these procedures, the aorta and the caval vein located in the retroperitoneum would be exposed. After which, dissection should proceed cranially until the superior mesenteric artery root and left renal vein are visualized (Fig. 56.1b). One should keep in mind the extent of mobilization should not go beyond the superior mesenteric artery root. The origin of the superior mesenteric artery is generally identified by a vessel loop during the retroperitoneal margin dissection. The superior mesenteric artery also needs to be identified in preparation of cross clamping of the artery in case of bowel congestion related to long superior mesenteric vein cross-clamping time or in case of the superior mesenteric artery bleeding. Following the method described, the bowel should be sufficiently mobilized for vein reconstruction.

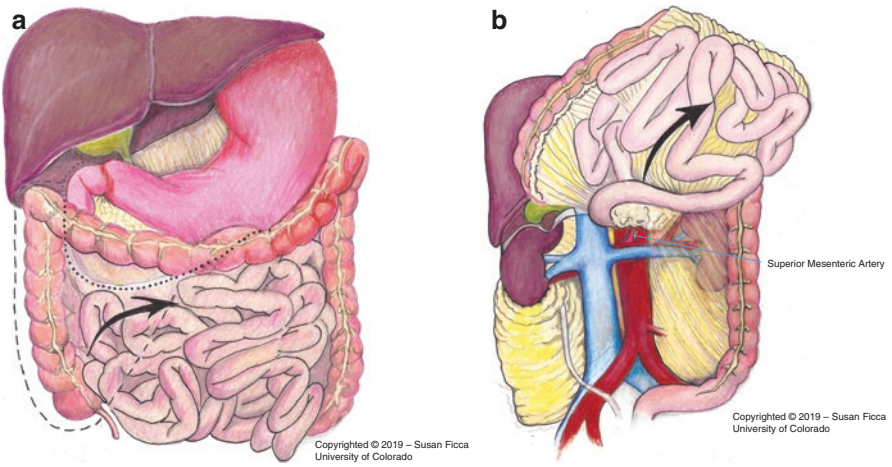

Fig. 56.1 Cattell-Braasch maneuver. The cecum, right colon, and right colonic flexure are entirely mobilized (**a**). The root of the small bowel is also mobilized by following an avascular plane from the retroperitoneum together with the Treitz ligament (**b**)

56.3 Hepatic Arteries and Celiac Trunk Resection with Reconstruction

56.3.1 End-to-End Anastomosis

When the tumor involves the hepatic artery or the celiac trunk, the presence of a free margin at the hepatoduodenal ligament or the celiac trunk origin from aorta should be identified for vascular reconstruction, respectively. When the tumor invades a short-segment of the hepatic artery (Fig. 56.2), the segment of the hepatic artery should be resected with the tumor, and the hepatic artery could be subsequently reconstructed by end-to-end anastomosis [11] (Fig. 56.3).

56.3.2 Rotation of the Splenic Artery

When the tumor involves a long-segment of the hepatic artery or the celiac trunk, total pancreatectomy with rotation (transposition) of the splenic artery is recommended for artery reconstruction. This procedure is performed by mobilizing the persevered splenic artery on the celiac trunk axis and anastomosing the end of the splenic artery with the distal cut margin of the resected hepatic artery (Fig. 56.4). Total pancreatectomy prevents the occurrence of pancreas fistula and its potentially fatal complications that can affect the intactness of artery anastomosis.

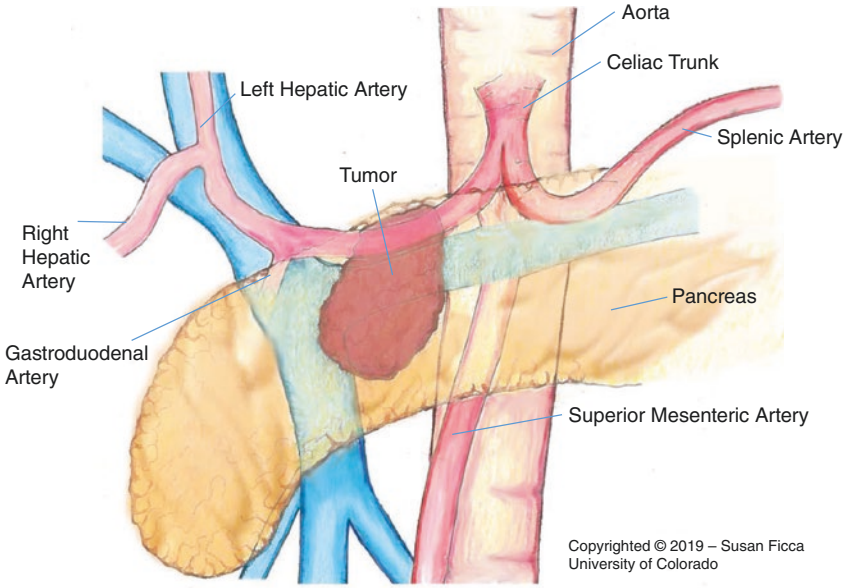

Fig. 56.2 Pancreatic head cancer invading the common hepatic artery. When the common hepatic artery is involved, the presence of a free margin at the hepatoduodenal ligament or the celiac trunk origin from aorta should be identified before vascular reconstruction

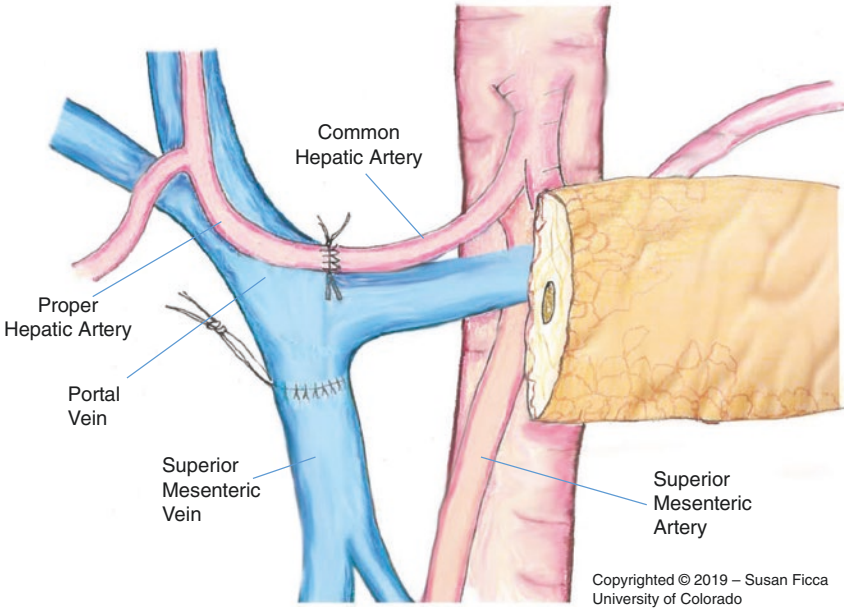

Fig. 56.3 End-to-end anastomosis of the hepatic artery. When the hepatic artery is involved, the involved segment of the hepatic artery should be resected with the tumor, and the hepatic artery could be reconstructed by end-to-end anastomosis

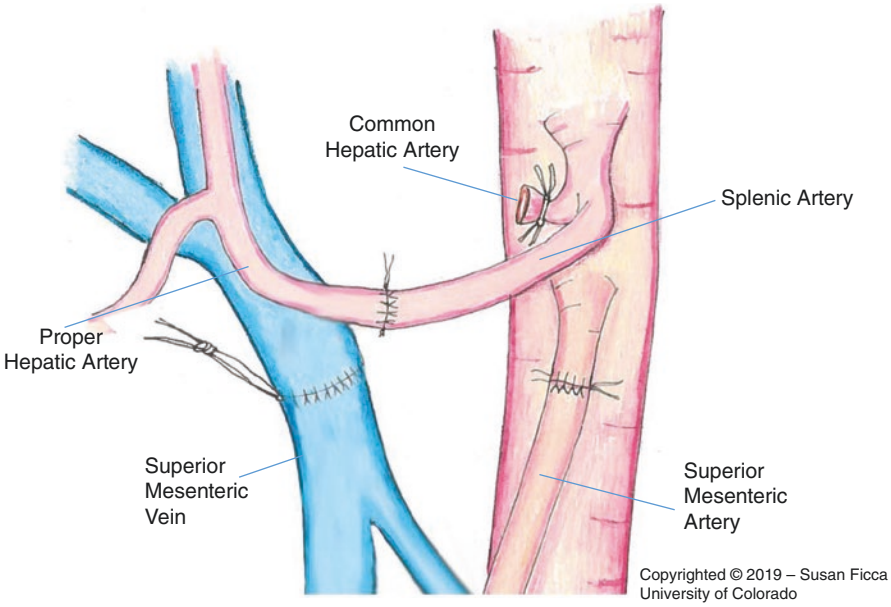

Fig. 56.4 Rotation of the splenic artery and the superior mesenteric artery reconstruction. When a long segment of the hepatic artery is involved, total pancreatectomy with rotation (transposition) of the splenic artery for artery reconstruction could be performed. The persevered splenic artery at the celiac trunk is mobilized and anastomosed to the distal cut margin of the resected hepatic artery. When the superior mesenteric artery is involved, a 5 mm free margin after resection is needed for reconstruction. For reconstructing of the resected superior mesenteric artery, end-to end anastomosis can be performed with Cattell-Braasch maneuver and bowel hypothermia

56.3.3 Graft Interposition

When the tumor involves a long-segment of the hepatic artery and the splenic artery needs to be resected or preserved, an alternative structure is required for artery reconstruction. In such cases, anastomosis of the hepatic artery and the celiac trunk can be achieved with an interposition saphenous vein graft, unless distal pancreatectomy with celiac axis resection (DP-CAR) procedure is performed (Fig. 56.5).

56.4 Hepatic Artery and Celiac Trunk Resection Without Reconstruction (Distal Pancreatectomy with Celiac Axis Resection, Modified Appleby Procedure)

When locally advanced PDAC involves the pancreas body, the procedure of DP-CAR could be considered. DP-CAR is performed to create negative microscopic margins at the celiac trunk, nerve plexus, and retroperitoneal tissue

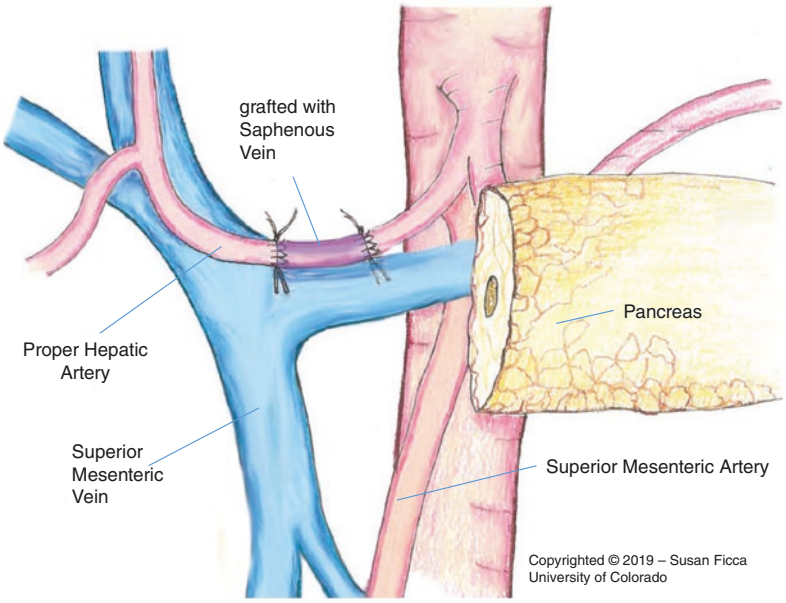

Fig. 56.5 Graft interposition. When the celiac trunk and the splenic artery are simultaneously involved, anastomosis of the hepatic artery and the celiac trunk can be achieved with an interposition saphenous vein graft

[12–14]. This procedure is a derivative of the Appleby procedure that was originally invented for radical lymph node dissection used in treating advanced gastric cancer [15]. Arterial reconstruction is not necessary for this procedure, since the collateral pathways coming from the superior mesenteric artery, pancreatoduodenal arcades, and the gastroduodenal artery can supply the hepatobiliary system (Fig. 56.6).

56.5 Superior Mesenteric Artery Resection

In the setting of tumor involvement of the superior mesenteric artery and artery reconstruction is considered, surgeons need to assess the possibility of obtaining tumor-free margins of at least 5 mm at the mesentery and aorta after resection. Intraoperative frozen section analysis needs to be performed to exclude arterial margin involvement. After performing the superior mesenteric artery resection, reconstruction of this artery can be achieved through end-to-end anastomosis, in combination with tension-reducing Cattell-Braasch maneuver and local hypothermia [16] (Fig. 56.4).

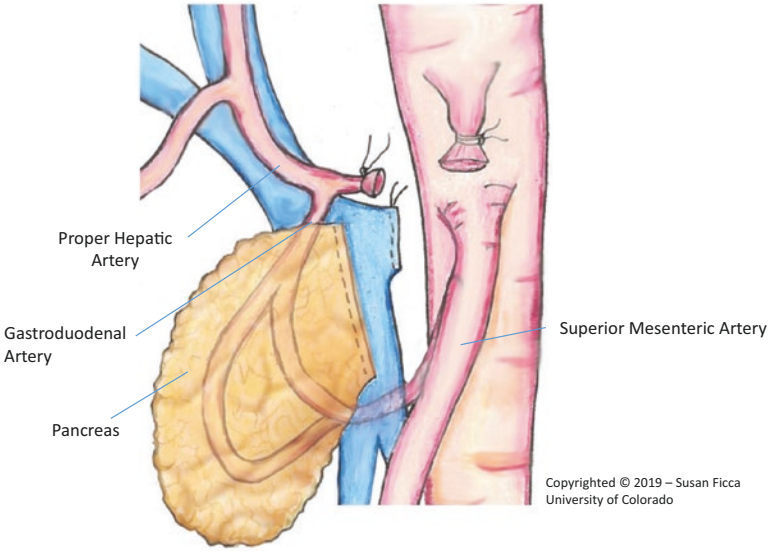

Fig. 56.6 Hepatic artery and celiac trunk resection without reconstruction (distal pancreatectomy with celiac axis resection, modified Appleby procedure). Arterial reconstruction is not necessary in DP-CAR, since hepatobiliary arterial blood supply can be maintained by the collateral pathways originated from the SMA, pancreatoduodenal arcades, and the gastroduodenal artery

56.6 Combination Arterial and Venous Resection

56.6.1 2 Vessels (Superior Mesenteric Artery, Superior Mesenteric Vein)

When there is a concurrent tumor involvement of the superior mesenteric artery and superior mesenteric vein/portal vein, resection and end-to-end anastomotic vessel reconstruection of the respective vasculatures could be performed. Bowel mobilization allows reconstruction of vessels irrespective of the remaining length of the vessels after resection [8].

56.6.2 2 Vessels (Hepatic Artery, Superior Mesenteric Vein): Splenic Rotation

When the tumor simultaneously involving the hepatic artery and superior mesenteric vein/portal vein, the hepatic artery should be resected first to minimize the risk of liver ischemia. Unless the pancreas is markedly fibrotic, total pancreatectomy is usually performed to avoid leakage.

56.6.3 3 Vessels (Hepatic Artery, Superior Mesenteric Artery, Superior Mesenteric Vein): Interposition

Similar to the situation in which there is a concurrent tumor invasion of the hepatic artery and superior mesenteric vein or portal vein, the hepatic artery should be resected first to prevent liver ischemia when the hepatic artery, the superior mesenteric artery, and the superior mesenteric vein/portal vein are concurrently involved. Total pancreatectomy is generally performed for the same reason to prevent leakage (Fig. 56.4).

56.7 What's New in Arterial Resection?

Although the practice of pancreatectomy with major peripancreatic artery resection is still debatable, recent literature has demonstrated that there are survival advantages associated with this procedure compared to palliative procedures [17]. In fact, studies have shown that survival outcome associated with artery resection is superior to the that of vein-artery resection [7]. It has been speculated that the patients' prognosis and survival outcomes are more associated with the biological characteristics of the tumor, rather than the vessels that involved. Hence, factors such as the aggressiveness of tumor development and response of the tumor to systemic therapy should be taken into consideration prior to performing surgical treatment [7].

Modern multi-drug chemotherapy has raised the median survival rate of patients with primary resectable PDAC from 35 to 54 months. With the emergence of these effective systemic therapy, the implementation of artery resection in may become more questionable [18].

However, patients, who received systemic therapy in conjunction with pancreatectomy with arterial resection, have been reported to have improved long-term survival outcome that is nearly equivalent to that of those with primary resectable PDAC without artery involvements [11, 19]. According to a cohort of 118 patients from 1990–2017, the 5-year-survival rate associated with pancreatectomy with arterial resection were 11.8% [20]. Del Chiaro et al. reported that a 5-year survival of patients who underwent pancreatectomy with arterial resection (50% of whom underwent neoadjuvant treatment) were superior to that of those who underwent palliative care due to unresectability (23.4% vs. 0%, P = 0.003) [11]. In the same study, the complication rate of pancreatectomy with arterial resection was 38.2% and mortality rate was 2.9%. Study conducted by Tee et al. showed that the median survival period of patients who underwent pancreatectomy with arterial resection following neoadjuvant treatment was longer than that of those who underwent upfront resection (53.6 months vs. 16.6 months, p = 0.038, log-rank test) [19]. Although these favorable results could be associated with the advancement in pancreatic surgery and improved peri-operative management, it is important to

note that incorporation of modern chemotherapeutics in PDAC treatment is also one of the key variables in the improvement of treatment outcome. Modern systemic chemotherapeutics for the treatment of PDAC can be an effective tool in selecting surgical candidacy, as those with better response to chemotherapy generally will have better survival outcomes after undergoing pancreatectomy with or without arterial resection. Since there is a lack of reliable predictors of resectability [21, 22], and there are some studies that support the practice of radical pancreatectomy associated with artery resection [11, 19], several publications have advocated that all borderline resectable/locally advanced tumor cases should undergo surgical exploration after neoadjuvant treatment, whether or not radiologic imaging show effective treatment response [23, 24].

56.8 Management After Vascular Resection

Currently, very few data address the peri-operative management of patients who underwent pancreatectomy with arterial resection. The few series reported in literature are either missing or presenting different peri-operative managements. In this chapter we will describe our approach, modified from other surgical procedures, based on our practice and experience that still require validation through studies.

56.8.1 Before Surgery

- Normal subcutaneous low molecular weight heparin should be given for prophylaxis of deep vein thrombosis.
- No epidural analgesia should be given to avoid intra- and post-operative hypotension.

56.8.2 During Surgery

- Systemic heparinization (5000 IU i.v.) should be given only in case of arterial resection, but not in isolated vein resection.

56.8.3 After Surgery

- Subcutaneous low molecular weight heparin prophylaxis should be given for at least 2 weeks.

– In case with complex vascular reconstruction, prothrombin time should be maintained at 40 to 60 s for 5 days via heparin infusion. After which, heparin should be given subcutaneously.
– Low dose aspirin should be given from day 4 to 5 and is maintained indefinitely.

56.9 Learning Curve and Training

To the best of our knowledge, there are no reports, data or recommendations for training of pancreatectomy with artery reconstruction. Therefore, multiple aforementioned concepts in this text are based on personal opinions and experience.

As for any low-level-evidence practice regardless of specialty, the indication and the selection of patients for pancreatectomy with arterial resection is crucial. Before starting a program for the surgical treatment of locally advanced PDAC, a competent multidisciplinary team, involving oncologists, radiologists, endoscopists, gastroenterologists, pathologists, anesthesiologists, surgeons and other experts in this field, should be active. These cases should be discussed in a dedicated multidisciplinary pancreas specific clinic.

The decision to proceed with these operations should be based on the patient's prognosis and their preoperative condition that determines whether they are fit to undergo surgery.

In addition, according to the promising data showing constantly improving therapeutic effects of neoadjuvant therapy, performing arterial resection by pancreatic surgeons will eventually become necessary for better survival outcome of the patients. Currently, there are very few centers in the world with training programs that are designed for these kinds of procedures. Some surgical fellowships have incorporated training of peripancreatic artery resection and reconstruction in their program (https://medschool.cuanschutz.edu/surgery/specialties/surgical-oncology/education).

Before the establishment of multiple training programs focusing on these procedures, we suggest two safe methods of learning the procedure of pancreatectomy with artery resection and reconstruction:

1. Involvement in training for both HPB surgical oncology and transplant is recommended. This European approach in training emphasizes on combining competency required in Surgical Oncology and the training needed for handling abdominal vessels, including small visceral vessels.
2. Creating a surgical team in which a surgical oncologist can collaborate with vascular surgeon and/or transplant surgeon is recommended. However, this approach, can present some disadvantage, as described in several series, since surgeons from different teams may fail to notice important information related to the part of the surgery that they will not perform, if there is no adequate communication amongst the teams.

While training programs are being established for these procedures, we believe that these are the two minimum requirements needed to perform these kinds of procedures.

56.10 Conclusion

Even if more studies are showing that local anatomical details, such as artery infiltration, are not the most important prognostic factor in PDAC and that prognosis of the disease is more related to tumor biology, artery resections during pancreatectomy should not be considered for every patient [25]. In order to have good treatment results, the selection criteria of patients are crucial. Patients who could potentially benefit from an arterial resection should be referred to experienced centers. Even though only few studies indicate that pancreatectomy with artery resection should become a routine, we still need to prepare ourselves to perform these surgeries since more patients will need to undergo artery resections due to the emergence of more effective systemic treatment for PDAC.

The management of these patients should be standardized, and surgeons should receive a dedicated training. High volume of pancreatic surgery cases is necessary, but not enough to develop a program for the surgical treatment of locally advanced PDAC. Therefore, in this area of pancreatology, we could consider the implementation of centralization.

References

1. Fortner JG. Regional resection of cancer of the pancreas: a new surgical approach. Surgery. 1973;73(2):307–20.
2. Fortner JG, Kim DK, Cubilla A, Turnbull A, Pahnke LD, Shils ME. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg. 1977;186(1):42–50.
3. Warren KW, Choe DS, Plaza J, Relihan M. Results of radical resection for periampullary cancer. Ann Surg. 1975;181(5):534–40.
4. Mackie JA Jr, Rhoads JE. Pancreaticogastrostomy following radical pancreaticoduodenal resection. Bull Soc Int Chir. 1975;34(6):611–4.
5. Herter FP, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and periampullary cancer. Ann Surg. 1982;195(3):274–81.
6. Shapiro TM. Adenocarcinoma of the pancreas: a statistical analysis of biliary bypass vs Whipple resection in good risk patients. Ann Surg. 1975;182(6):715–21.
7. Boggi U, Del Chiaro M, Croce C, Vistoli F, Signori S, Moretto C, et al. Prognostic implications of tumor invasion or adhesion to peripancreatic vessels in resected pancreatic cancer. Surgery. 2009;146(5):869–81.
8. Del Chiaro M, Segersvard R, Rangelova E, Coppola A, Scandavini CM, Ansorge C, et al. Cattell-Braasch maneuver combined with artery-first approach for superior mesenteric-portal vein resection during pancreatectomy. J Gastrointest Surg. 2015;19(12):2264–8.
9. Kleive D, Sahakyan MA, Berstad AE, Verbeke CS, Gladhaug IP, Edwin B, et al. Trends in indications, complications and outcomes for venous resection during pancreatoduodenectomy. Br J Surg. 2017;104(11):1558–67.

10. Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T, et al. Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. Br J Surg. 2016;103(12):1683–94.
11. Del Chiaro M, Rangelova E, Halimi A, Ateeb Z, Scandavini C, Valente R, et al. Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer. HPB (Oxford). 2019;21(2):219–25.
12. Kondo S, Katoh H, Hirano S, Ambo Y, Tanaka E, Okushiba S, et al. Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally advanced cancer of the pancreatic body. Langenbecks Arch Surg. 2003;388(2):101–6.
13. Nakamura T, Hirano S, Noji T, Asano T, Okamura K, Tsuchikawa T, et al. Distal pancreatectomy with en bloc celiac axis resection (modified Appleby procedure) for locally advanced pancreatic body cancer: a single-center review of 80 consecutive patients. Ann Surg Oncol. 2016;23(5):969–75.
14. Oba A, Inoue Y, Sato T, Ono Y, Mise Y, Ito H, et al. Impact of indocyanine green-fluorescence imaging on distal pancreatectomy with celiac axis resection combined with reconstruction of the left gastric artery. HPB (Oxford). 2019;21(5):619–25.
15. Appleby LH. The coeliac axis in the expansion of the operation for gastric carcinoma. Cancer. 1953;6(4):704–7.
16. Westermark S, Rangelova E, Ansorge C, Lundell L, Segersvärd R, Del Chiaro M. Cattell-Braasch maneuver combined with local hypothermia during superior mesenteric artery resection in pancreatectomy. Langenbecks Arch Surg. 2016;401(8):1241–7.
17. Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Buchler MW, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg. 2011;254(6):882–93.
18. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
19. Tee MC, Krajewski AC, Groeschl RT, Farnell MB, Nagorney DM, Kendrick ML, et al. Indications and perioperative outcomes for pancreatectomy with arterial resection. J Am Coll Surg. 2018;227(2):255–69.
20. Bachellier P, Addeo P, Faitot F, Nappo G, Dufour P. Pancreatectomy with arterial resection for pancreatic adenocarcinoma: how can it be done safely and with which outcomes?: a single institution's experience with 118 patients. Ann Surg. 2020;271(5):932–40.
21. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg. 2015;261(1):12–7.
22. Wagner M, Antunes C, Pietrasz D, Cassinotto C, Zappa M, Sa Cunha A, et al. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. Eur Radiol. 2017;27(7):3104–16.
23. Michelakos T, Pergolini I, Castillo CF, Honselmann KC, Cai L, Deshpande V, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2019;269(4):733–40.
24. Rangelova E, Wefer A, Persson S, Valente R, Tanaka K, Orsini N, et al. Surgery improves survival after neoadjuvant therapy for borderline and locally advanced pancreatic cancer: a single institution experience. Ann Surg. 2019. https://doi.org/10.1097/SLA.0000000000003301. Epub ahead of print. PMID: 30946073.
25. Oba A, Croce C, Hosokawa P, Meguid C, Torphy RJ, Al-Musawi MH, et al. Prognosis based definition of resectability in pancreatic cancer: a road map to new guidelines. Ann Surg. 2020. https://doi.org/10.1097/SLA.0000000000003859. Epub ahead of print. PMID:32149822.

Chapter 57
Laparoscopic Pancreatoduodenectomy for Pancreatic Cancer

Ioannis Triantafyllidis and David Fuks

Take Home Messages
- Cases should be carefully selected (resectable tumors, no vascular invasion).
- High-quality cross-sectional imaging and identification of anatomic variants (i.e., replaced/aberrant right hepatic artery) and vascular involvement.
- Good preoperative planning.

Pearls and Pitfalls
- Placing the patient in reverse Trendelenburg position facilitates better exposure of the main anatomical structures.
- Use intraoperative ultrasound to assess the tumor margins and its relationship with vascular structures.
- Grasping or any traction applied on gastroduodenal artery should be avoided at all costs due to the fragility of the vessel.
- Be aware of the presence of a replaced or aberrant right hepatic artery.

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- Pay attention to the small mesenteric tributaries of the uncinate process as they can easily be avulsed resulting in troublesome hemorrhage.
- Create the anastomoses at the beginning of the learning curve via a mini laparotomy. Furthermore, portal vein resection and/or reconstruction, may be accomplished through this laparotomy.
- In cases of soft and fragile pancreatic remnant or small sized pancreatic duct prefer a triple purse-string telescoped pancreatogastrostomy.
- Use a falciform ligament flap to cover the stump of the gastroduodenal artery.

Future Perspectives

- Future prospective studies with a large patient cohort for ensuring adequate patient selection.
- Modifications of this innovative procedure, and perioperative management are necessary to demonstrate the efficacy and effectiveness of laparoscopic pancreatoduodenectomy.
- Technical developments, or improvement of the existing, is necessary, pertaining to sophisticated instruments may facilitate an easier and safer pancreatojejunostomy, especially if laparoscopically performed.
- Randomized control trials are necessary to clarify the value of portal vein resection in pancreatoduodenectomy for pancreatic cancer.

57.1 Introduction

Laparoscopic distal pancreatectomy is widely acknowledged as an efficient alternative compared to its open counterpart in terms of postoperative morbidity and oncological outcomes [1]. However, laparoscopic pancreatoduodenectomy is a technically demanding procedure, and there is no consensus in the literature regarding its' oncologic efficacy and safety when applied for the treatment of pancreatic cancer, although, single-center studies have proven the feasibility and benefits of laparoscopic pancreatic surgery [2, 3]. Despite the fact that the first laparoscopic pancreatoduodenectomy was performed by Gagner and Pomp in 1994, the procedure was not popularized. Nevertheless, a minimally invasive pancreatoduodenectomy has the potential to reduce inflammatory response, enhance recovery, decrease postoperative pain, morbidity and in-hospital stay, improve the quality of life and hence facilitate the implementation of adjuvant therapy. For these reasons, implementation of laparoscopic pancreatoduodenectomy during the last decade has been characterized by a sharp rise in interest and current results are promising.

57.2 Patient Selection

Adequate preoperative assessment with multidetector computed contrast enhanced tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen are of paramount importance in determining whether a patient is a candidate for an open or laparoscopic pancreatoduodenectomy, or not suitable for any operation.

Most patients with periampullary neoplasms are eligible for a laparoscopic pancreaticoduodenectomy. Borderline cases of pancreatic adenocarcinoma, obesity, chronic pancreatitis, administration of neoadjuvant chemotherapy and/or radiotherapy, large tumors (>3 cm) or previous laparotomies are relative contraindications [4–6]. Apart from the traditional contraindications of laparoscopic surgery, locally advanced neoplasms with involvement of major venous or long porto-mesenteric segments necessitating resections with reconstruction, or cases requiring anatomical hepatectomy, constitute an absolute contraindication to laparoscopic pancreatoduodenectomy [4–7], although several highly specialized centers of excellence occasionally offer laparoscopic pancreatoduodenectomy even in this setting [8].

57.3 Surgical Technique

Currently, the surgical approaches for laparoscopic pancreatoduodenectomy range from a totally laparoscopic approach when both the dissection and the reconstruction of all the anastomoses (pancreaticojejunostomy, hepaticojejunostomy, gastrojejunostomy) are performed intracorporeally to the most commonly reported hybrid laparoscopic-assisted techniques when the dissection is performed laparoscopically and the reconstruction is done through a mini-laparotomy which is also used for specimen extraction [9].

57.3.1 Positioning of the Patient and Trocars

The patient under general anesthesia is placed in the supine lithotomy position, with the legs abducted (French position). The surgeon is positioned between the legs of the patient and the first and second assistant to the left and right side of the patient. The upper extremities are covered with soft pads and are extended less than 60° to avoid any potential injury to the brachial plexus.

Pneumoperitoneum is established through a 12 mm optical periumbilical trocar, where a 30° laparoscope is introduced, and is usually maintained at 12 mmHg. The laparoscope should be placed, in a patient with normal Body Mass Index, slightly to the right and above the umbilicus, to align with the superior mesenteric vein and facilitate the best exposure of the uncinate process. Under direct vision, five additional ports are placed: one 12-mm port in midpoint between the xiphoid process and the umbilicus for

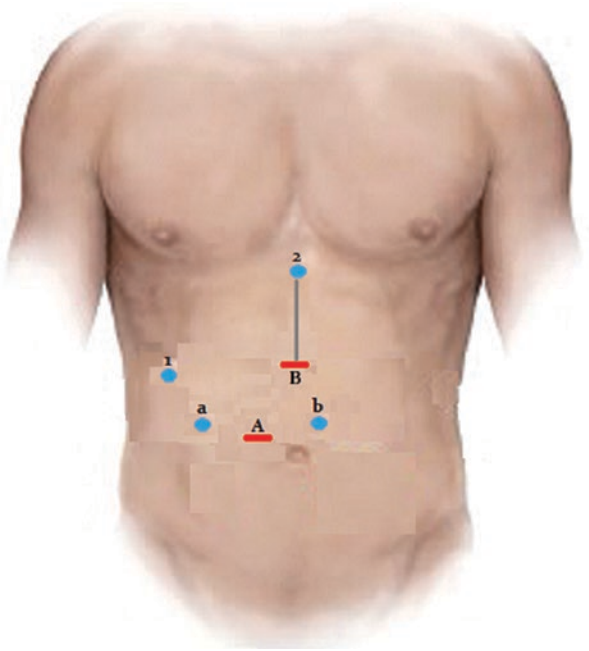

Fig. 57.1 Trocar positioning during laparoscopic pancreatoduodenectomy. (**a**, **b**) 12-mm trocar used for laparoscope/stapler insertion. (**a**, **b**) 5-mm working trocars. 1,2: 5-mm trocar exposure trocars. Gray line: mini laparotomy for the specimen's extraction and reconstruction (hybrid technique)

the laparoscopic ultrasound device and/or endoscopic stapler, and four 5-mm trocars—two working channels in the paraumbilical/pararectal region on either side of the midline (usually along the mid-clavicular line) and two for exposure and lateral traction as needed: one in the right upper quadrant (usually 2 cm below the inferior costal margin) and the remaining subxiphoidically in the midline (Fig. 57.1).

Placing the patient in reverse Trendelenburg position facilitates better exposure of the main anatomical structures. Furthermore, abraided Silk 0 transfixing stitch piercing the round ligament, inserted subxiphoidically, provides an efficient suspension of the liver (Fig. 57.2).

57.3.2 Intraoperative Assessment of Tumor Resectability

After port placement a general inspection of the peritoneal cavity is performed in order to rule out any peritoneal or liver metastases. Any suspicious peritoneal or liver nodule as well as lymph nodes at the left side of the superior mesenteric artery and/or the aortocaval space are sent for frozen section [10]. Metastases in the aforementioned structures preclude the continuation of the operation. Intraoperative

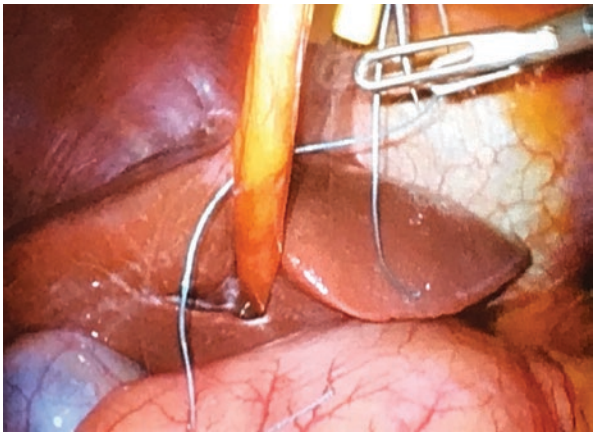

Fig. 57.2 A braided Silk 0 transfixing stitch piercing the round ligament, inserted subxiphoidically with a suture passer, provides an efficient suspension of the liver

ultrasound is used to assess the tumor margins and its relationship with the major vessels and surrounding structures to confirm the final resectability of the tumor [11]. However, inter-aorto-caval lymphadenectomy remains a controversial issue in the treatment of periampullary cancer [12].

57.3.3 Cholecystectomy

The first step of the operation is a laparoscopic cholecystectomy. Any adhesions are taken down with ultrasonic shears and/or scissors. The cystic duct and cystic artery are divided, and the gallbladder is removed using an extraction bag.

57.3.4 Dissection of the Right Colon and Duodenum

The gastrocolic ligament is opened in order to enter the lesser sac and expose the retroperitoneal area and ultimately the pancreas. Division of the gastrocolic ligament is performed below the gastroepiploic vessels using an energy device (i.e. ultrasonic shears, LigaSure, etc) or bipolar diathermy along with scissors. Subsequently, under appropriate cephalad traction by grasping the stomach antrum or body with atraumatic forceps, any adhesions present between the posteriorsurface of the stomach and the anterior surface of the pancreas, are taken down, leading to direct visualization of the pancreas. We continue dissection laterally to fully mobilize the hepatic flexure and exposing the duodenum. Right colon mobilization facilitates an easier mobilization of the duodenum and control of gastrocolic trunk

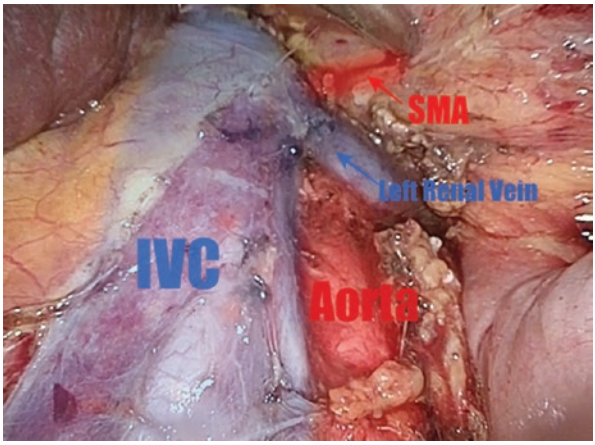

Fig. 57.3 Aorto-caval dissection. *IVC* inferior vena cava, *SMA* superior mesenteric artery

of Henle as well as of the superior mesenteric vein and first jejunal venous branch. Next, a Kocher maneuver is performed to the level of the left renal vein, taking all the retroperitoneal attachments off the pancreas and exposing the medial and inferior borders of the superior mesenteric artery. During the Kocher maneuver, we ensure gentle traction on the duodenum in order to avoid an inadvertent perforation. A wide Kocherization allows an excellent exposure of the inferior vena cava and aortocaval and right celiac plexus dissection (Fig. 57.3).

57.3.5 Dissection of the Portal Venous Confluence

The peritoneum overlying the inferior border of the pancreas is opened and dissected in order to identify the infrapancreatic superior mesenteric vein. Blunt dissection is carried on along the anterior surface of the superior mesenteric vein, progressively separating the vein from the posterior aspect of the pancreatic neck and eventually leading to the identification of the spleno-mesenteric confluence. Ligation of the gastrocolic trunk of Henle using an energy device is mandatory prior beginning the creation of the retropancreatic "tunnel" from below (Fig. 57.4). During this step, the laparoscopic approach offers a significant advantage represented by the magnified visualization of the "tunnel". Injury of the porto-mesenteric veins should be avoided at all costs by very gentle preparation.

57.3.6 Dissection of the Hepatoduodenal Ligament

We are now proceeding to the dissection of the common and proper hepatic artery. This step ensures proper recognition of the gastroduodenal artery before its transection. An adequate lymph node clearance of the hepatoduodenal ligament is

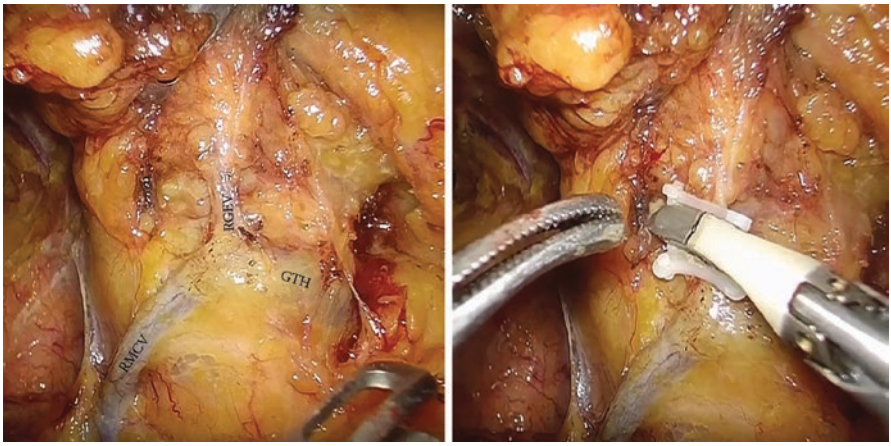

Fig. 57.4 Ligation of the gastrocolic trunk of Henle

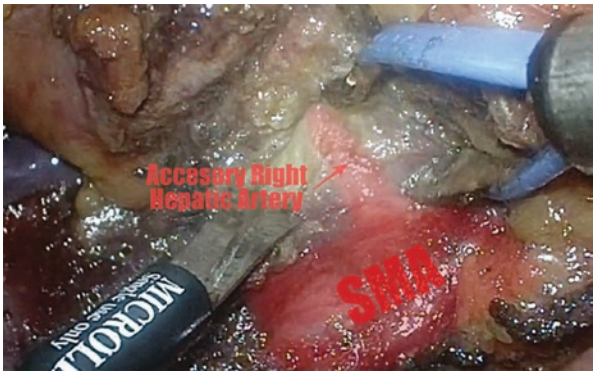

Fig. 57.5 Accessory right hepatic artery arising from the SMA (Superior mesenteric artery)

performed. The removal of the common hepatic artery lymph node further facilitates the visualization of the gastroduodenal artery which is then skeletonized. Grasping or any traction on gastroduodenal artery should be avoided at all costs due to the fragility of the vessel. Additionally, care should be taken in order to avoid any avulsion to the superior anterior pancreaticoduodenal artery. Above all, a hepatic artery injury should be avoided during this step by using scissors for dissection of the hepatic artery. The common hepatic artery is lifted by a vascular band (about 8 cm in length) in order to facilitate the dissection of surrounding lymph nodes. We then identify the common bile duct and all lymphatic tissue lateral and posterior to it is cleared inferiorly towards the pancreas. The surgeon should be aware of the presence of a replaced or aberrant right hepatic artery (Fig. 57.5), which will be identified posterior to the common bile duct. The common bile duct is transected either with an endoscopic stapler to avoid bile spillage or with electrocautery or cold scissors. In the latter cases an endo-bulldog clamp should be placed to secure its proximal aspect. Usually, the common bile duct is transected 2–3 cm cephalad the

superior edge of the pancreas. “Cold” transection preserves a normal bile duct wall for the subsequent bilio-enteric anastomosis.

57.3.7 Transection of the Jejunum and the Stomach

The next step is stomach and jejunal transection. The ligament of Treitz is identified, mobilized from its retroperitoneal attachments and divided, allowing the proximal jejunum to be pulled underneath the superior mesenteric artery. The jejunum is transected with a linear endoscopic stapler, approximately 15–20 cm distal to the duodeno-jejunal flexure and the mesentery is divided with an energy device at the border of the mesentery and serosa. The transection of the jejunal mesentery is continued up to the uncinate process and the superior mesenteric vein. We then divide the greater omentum at the level of the gastric antrum, the right gastroepiploic artery is divided using bipolar diathermy or an energy device. The lesser omentum is opened and the stomach is transected with an endoscopic stapler just proximal to the pylorus. Alternatively to a Whipple pancreatoduodenectomy [13], a pylorus preserving pancreatoduodenectomy [14] may be performed and in such case, the duodenum is transected 2–3 cm distal to the pylorus, in order to preserve its function.

57.3.8 Ligation of the Gastroduodenal Artery and Completion of the Retropancreatic “Tunnel”

At this step, gastroduodenal artery is ligated with clips and/or stiches, near its origin from the common hepatic artery just above the superior margin of the pancreas. Prior to gastroduodenal artery ligation, common hepatic artery flow is confirmed on Doppler after occlusion of the gastroduodenal artery using an endo-bulldog. The supra-pancreatic portal vein is identified at the apex of the triangle formed by the common hepatic artery, gastroduodenal artery, and the superior border of the pancreas. The avascular plane between the posterior aspect of the pancreatic neck and the portal vein is developed in a cephalad-to-caudal direction, thereby completing the retro-pancreatic “tunnel” from above.

57.3.9 Transection of the Pancreas and Retroperitoneal Dissection

We can now proceed to pancreatic transection along the previously created “tunnel” with an energy device, laparoscopic linear stapler or with electro-cautery. However, it seems important to perform a “cold” transection of the pancreatic duct with

scissors, 2–3 mm from the right side of the parenchymal transection line. This enables an easy future passage of the pancreatic juice. The pancreatic remnant is mobilized 2–3 cm to the tail, if a pancreaticojejunostomy is planned or furthermore (up to 4–5 cm) to the groove of the splenic artery on the posterior surface of the pancreas if a pancreatogastrostomy will be performed, and covered by a gauze in order to prevent the spillage of the pancreatic juice into the peritoneal cavity. When necessary, a frozen section of the transected section of the pancreas, is performed.

The inferior pancreaticoduodenal arcade is controlled and thereafter, both the duodenum and the first jejunal loop can easily be rotated under the mesenteric vessels. Pulling the jejunum underneath the ligament of Treitz—and not through a defect in the transverse mesocolon—avoids jejunal twisting that can be easily overlooked laparoscopically and provides a tension-free loop for reconstruction. The dissection continues towards the porto-mesenteric confluence by pulling the specimen upwards and to the right while dissecting and ligating all short vessels to the uncinate process. The uncinate process can be dissected free from the superior mesenteric artery using an energy device; however, occasionally it will require clips or ligature. We are now transecting the retroperitoneum along the superior mesenteric artery. The surgeon should pay attention to the small mesenteric tributaries to the uncinate process as they can easily be avulsed resulting in troublesome hemorrhage. Cephalad, we encounter and individually ligate the superior pancreaticoduodenal arcade. With the dissection along the superior mesenteric vessels, the mobilization of the specimen is completed (Fig. 57.6). The extraction of the specimen is performed using a laparoscopic endobag, through a mini laparotomy extended among the 5 mm and 12 mm trocars in the midline (Fig. 57.1) and after inserting a plastic wound protector.

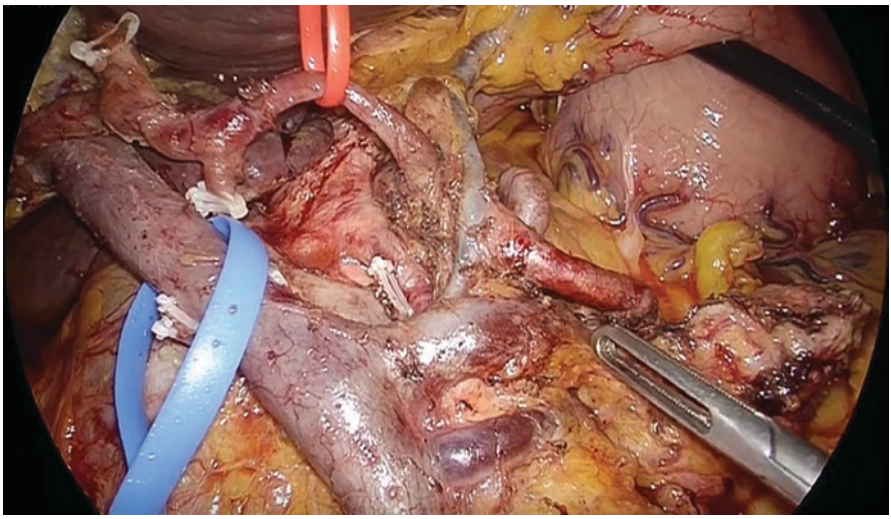

Fig. 57.6 Endoscopic view of the major vasculature of the surgical field after specimen's complete mobilization

57.3.10 Vascular Resection

The international study group of pancreatic surgery (ISGPS) guideline recommended straight forward resection in the presence of isolated and reconstructable portal-mesenteric vein involvement, in order to obtain an R0 resection [15]. Reconstruction is easier on the portal compared to the superior mesenteric vein because the portal vein is more superficial with longer distance from the mesentery and the mesocolon, has a thicker wall and is easier to be controlled. Resection should be performed, either in a wedge or cylindrical manner using cold scissors, after the specimen is extracted, because the exposure is better and vascular clamping is more effective as all venous collaterals are controlled. Although vascular clamping is prolonged compared to open pancreatoduodenectomy, it seems that clamping is better tolerated during the laparoscopic approach due to less mobilization and twisting of the intestine.

Extensive mobilization of porto-mesenteric and splenic confluence is mandatory. Thereafter, portal, superior mesenteric and splenic veins are controlled with vascular clamps. When a wedge or a cylindrical resection is performed, vascular reconstruction may be carried out with a monofilament continuous suture (e.g. Prolene 4/0 or 5/0). A defect between the proximal and distal vein edges >4 cm is considered an indication for interposition graft. After resection of the invaded venous segment, the distance between the cut edges is measured. A prosthetic graft is prepared based on this measurement. Reconstruction is performed in a caudal to cephalic manner. Caudal anastomosis is carried out after the graft and the vein are rotated 360° with a monofilament running suture while the cephalad anastomosis is performed from the posterior wall and then shifted to the anterior wall with a continuous suture as well. The graft is flushed with heparin solution after the reconstruction is completed. Postoperative thromboprophylaxis (with low molecular weight heparin initially and thereafter with warfarin) is of paramount importance for the graft patency [16].

57.3.11 Reconstruction

The reconstruction phase is carried out either intracorporally or through the mini laparotomy performed for the specimen's extraction and encompasses the performance of a pancreaticojejunostomy, hepaticojejunostomy and a gastrojejunostomy or duodenojejunostomy. It is advisable to create the anastomoses at the beginning of the learning curve via a mini laparotomy. Management of the pancreatic stump is the real key point of the entire procedure. Duct occlusion is associated with unacceptable incidence of pancreatic fistula. Currently, the majority of surgeons performs a pancreatojejunostomy rather than a pancreatogastrostomy, mainly due to the technical difficulty of the latter. Furthermore, a pancreatogastrostomy obstacles the creation of a laparoscopic gastrojejunostomy. Several variations of a pancreaticojejunostomy have been described: two-layer [17–19] or one-layer end-to-side duct-to-mucosa [20], one-layer end-to-end intussuscepting [21] or end-to-side

dunking anastomosis in a single -running or interrupted- layer or up to four layers of mattress sutures [22].

For the pancreatojejunostomy, we perform a two-layer end-to-side duct to mucosa anastomosis in all cases. The free end of a 20–30 cm jejunum loop is brought in proximity to the pancreatic stump in a retro-mesocolic fashion. It is necessary to check the position of jejunum's mesentery in order to avoid any torsion. The anastomosis begins with the construction of the posterior trans-pancreatic/seromuscular anastomotic row, which is fashioned using a single-layer synthetic absorbable monofilament suture (polydioxanone 4/0). The jejunum loop is stitched 4–6 cm distal from the stump in the middle of the posterior semi-circle. The pancreatic stump is stitched approximately 1.5–2.0 cm from the cut edge and 0.5 cm from the inferior part. The distance between sutures is 0.5–1.0 cm. Electrocautery or harmonic scalpel is utilized to create a small (2–3 mm) enterotomy in the jejunum. Thereafter, a duct-to-mucosa pancreaticojejunostomy is created using a synthetic absorbable monofilament suture (polydioxanone 5/0) in an interrupted fashion. Six to eight sutures are usually placed, depending on duct size. Implementation of a pancreatic stent is not mandatory in our opinion. However, trans-anastomotic stenting, either internal or external, still remains a controversial issue in pancreatic surgery. The anterior row is performed in the same manner as the posterior one (parallel to the posterior row of the pancreas). However, in cases of soft and fragile pancreatic remnant or small sized pancreatic duct we prefer a triple purse-string telescoped pancreatogastrostomy, usually via the mini laparotomy [23]. In such cases the reconstruction begins with the bilio-enteric anastomosis and thereafter the pancreatogastrostomy and finally gastrojejunostomy is performed.

The completion of a pancreaticojejunostomy is followed by the construction of an end-to-side bilio-enteric anastomosis using interrupted 4/0 synthetic absorbable monofilament sutures in cases of a narrow (<5 mm) bile duct. The posterior row of the anastomosis is fashioned first and usually requires three to four interrupted sutures. Subsequently, the anterior row of the hepaticojejunostomy is constructed in a similar manner. Alternatively, the anastomosis is performed by two running semicircular sutures 2 mm apart, in a clockwise fashion beginning at 9 and 3 o'clock, respectively. The incision of the jejunum wall is performed 10–15 cm distal to the pancreaticojejunostomy, using electrocautery or harmonic scalpel. In order to minimize the tension of the bilio-enteric anastomosis, it is advisable anchor the free end of the jejunal loop to the hilarplate using one or two interrupted stitches.

The gastrojejunostomy or duodenojejunostomy is the next and final reconstructive step. In both options the jejunum loop is pulled up in antecolic position and an anastomosis is performed 30–40 cm below the hepaticojejunostomy. The gastrojejunostomy is performed by a stapled technique in the lowest part of the gastric stump on the greater curvature and sutured closure of the common enterotomy is done in two layers. Alternatively, a "hand-sewn" gastrojejunostomy or end-to-side duodenojejunostomy in a one- or two-layered fashion can be formed.

Finally, the peritoneal cavity is inspected for bleeding, bile leakage, or remaining enterotomy defects. Two abdominal 19 French closed suction drains are placed close to the pancreatojejunostomy or pancreatogastrostomy through the foramen of

Winslow and the lesser sac. The greater omentum is pulled up to cover the pancreaticojejunostomy so that the gastrojejunostomy or duodenojejunostomy are not in direct contact with the pancreaticojejunostomy and is fixed in this position with clips or stiches. The falciform ligament is used to create a flap to cover the stump of the gastroduodenal artery, in order to prevent erosion in case of pancreatic leakage. The flap may be marked with a metallic clip for recognition if a postoperative angiography is needed. Abdominal wall fascial defects >5 mm are closed in a usual manner.

57.3.12 Postoperative Care

Most patients are transferred to the general ward and enhanced recovery after surgery (ERAS) protocols are implemented with conservative intravenous fluid administration according to standardized hemodynamic parameters and urine output as well as early diet advancement as tolerated. We do not typically leave a nasogastric tube, as there is no evidence to support its routine use. Drain output is measured for amylase level on postoperative day 1, 3 and 7 and drains are removed in the absence of a pancreatic fistula [24, 25].

57.4 Conclusions

Although more than 25 years have passed since its introduction, laparoscopic pancreatoduodenectomy remains a challenging, though technically demanding procedure with steep learning curve. One of the largest barriers of this complex procedure is the reconstruction phase with the creation of three separate anastomoses (pancreaticojejunostomy or pancreatogastrostomy, hepaticojejunostomy, and gastrojejunostomy). A hybrid approach may help surgeons—especially during the initial phase of the learning curve- to overcome the difficulties associated with a fully laparoscopic reconstruction, while retaining the advantages of laparoscopy. The cornerstone of the success is a thorough and careful selection of the patients. However, laparoscopic pancreatodudodenectomy should be evaluated in randomized controlled trials to establish its true benefit.

References

1. Magge D, Zeh HJ III, Moser AJ, et al. Comparative effectiveness of minimally invasive and open distal pancreatectomy for ductal adenocarcinoma. JAMA Surg. 2013;148(6):525–31.
2. Edwin B, Sahakyan MA, Abu Hilal M, et al. Laparoscopic surgery for pancreatic neoplasms: the European Association for Endoscopic Surgery Clinical Consensus Conference. Surg Endosc. 2017;31(5):2023–41.
3. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc. 1994;8:408–10.

4. Kendrick ML, Sclabas GM. Major venous resection during total laparoscopic pancreatoduodenectomy. HPB (Oxford). 2011;13(7):454–8.
5. Khatkov IE, Izrailov RE, Khisamov AA, et al. Superior mesenteric-portal veinresection during laparoscopic pancreatoduodenectomy. Surg Endosc. 2017;31(3):1488–95.
6. Delitto D, Luckhurst CM, Black BS, et al. Oncologic and perioperative outcomes following selective application of laparoscopic pancreatoduodenectomy for periampullary malignancies. J Gastrointest Surg. 2016;20(7):1343–9.
7. Boggi U, Amorese G, Vistoli F, et al. Laparoscopic pancreatoduodenectomy: a systematic literature review. Surg Endosc. 2015;29:9–23.
8. Kendrick ML, Sclabas GM. Major venous resectionduring total laparoscopic pancreatoduodenectomy. HPB (Oxford). 2011;13(7):454–8.
9. Palanivelu C, Jani K, Senthilnathan P, et al. Laparoscopic pancreatoduodenectomy: technique and outcomes. J Am Coll Surg. 2007;205:222–30.
10. Azagra JS, Arru L, Estévez S, et al. Laparoscopic pancreatoduodenectomy with /initial approach to the superior mesenteric artery. WideochirInne Tech Maloinwazyjne. 2015;10(3):450–7.
11. Corcione F, Pirozzi F, Cuccurullo D, et al. Laparoscopic pancreatoduodenectomy: experience of 22 cases. Surg Endosc. 2013;27(6):2131–6.
12. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the international study group on pancreatic surgery (ISGPS). Surgery. 2014;156(3):591–600.
13. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg. 1935;102:763–9.
14. Whipple AO. The rationale of radical surgery for cancer of the pancreas andampullary region. Ann Surg. 1941;114:612–5.
15. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155:977–88.
16. Wang X, Cai Y, Zhao W, et al. Laparoscopic pancreatoduodenectomy combined with portal-superior mesenteric vein resection and reconstruction with interposition graft: case series. Medicine (Baltimore). 2019;98(3):e14204.
17. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreatoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg. 2014;260(4):633–8; discussion 638–640.
18. Senthilnathan P, SrivatsanGurumurthy S, Gul SI, et al. Long-term results of laparoscopic pancreatoduodenectomy for pancreatic and periampullary cancer-experience of 130 cases from a tertiary-care center in South India. J Laparoendosc Adv Surg Tech A. 2015;25(4):295–300.
19. Stauffer JA, Coppola A, Villacreses D, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic adenocarcinoma: long-term results at a single institution. Surg Endosc. 2017;31(5):2233–41.
20. Dokmak S, Ftériche FS, Aussilhou B, et al. Laparoscopic pancreatoduodenectomy should not be routine for resection of periampullary tumors. J Am Coll Surg. 2015;220(5):831–8.
21. Delitto D, Luckhurst CM, Black BS, et al. Oncologic and perioperative outcomes following elective application of laparoscopic pancreatoduodenectomy for periampullary malignancies. J Gastrointest Surg. 2016;20(7):1343–9.
22. Wang M, Xu S, Zhang H, et al. Embedding pancreaticojejunostomy used in pure laparoscopic pancreatoduodenectomy for nondilated pancreatic duct. Surg Endosc. 2017;31(4):1986–92.
23. Addeo P, Rosso E, Fuchshuber P, et al. Double purse-string telescoped pancreaticogastrostomy: an expedient, safe, and easy technique. J Am Coll Surg. 2013;216(3):e27–33.
24. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an International Study Group (ISGPF) definition. Surgery. 2005;138:8e13.
25. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010;252(2):207–14.

Chapter 58
Robotic Surgery for Pancreatic Cancer

Long R. Jiao, Tamara M. H. Gall, and David N. Hakim

Take Home Messages
- Robotic surgery for pancreatic cancer is safe with reduced blood loss, length of stay, early physiological return to chemotherapy and equivocal if not better oncological outcome.

Pearls and Pitfalls
- With introduction of potential new robots to market over next few years, the cost will inevitably reduce to popularize robotic surgery till then it is currently used in a handful of fully competent HPB surgeons.

Future Perspectives
- Well-designed multi-centre randomised controlled trials comparing robotic pancreatic surgery to both open and laparoscopic techniques to identify the true benefit to this technique.

58.1 Introduction

Minimally invasive surgery (MIS) has had a profound impact on the surgical community over the last three decades, resulting in a transformation from conventional open surgical approaches in many surgical specialties. The benefit of MIS, including less blood loss, less blood transfusion requirements, reduced pain, reduced surgical

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trauma, and a faster return to functional activities, shortening length of hospital stay, is not disputed. There are, however, inherent challenges in laparoscopic surgery including compromised hand-eye coordination and the use of long rigid instruments, which restrict dexterity, and exaggerate the natural physiological tremor. This results in a long learning curve before laparoscopic surgery can be performed safely and effectively. Further, surgeons often experience significant discomfort and fatigue from the positioning required using laparoscopic techniques. Pancreatic surgery necessitates intricate dissections and complex sutured anastomoses, thus the uptake of minimally invasive surgery amongst pancreatic surgeons is significantly lower than other surgical specialties, and open surgery remains standard practice. Indeed, there is a considerable learning curve for laparoscopic pancreaticoduodenectomy (PD), which may be as high as 104 cases before expert proficiency is reached [1]. The LEOPARD-2 trial [2], which randomised patients to either laparoscopic or open PD, was terminated early due to a higher mortality directly related to laparoscopic PD, highlighting the potential problems with laparoscopic pancreatic surgery.

The disadvantages of laparoscopic surgery led to robotic solutions. In 2000, the Da Vinci robotic system (Intuitive Surgical Inc., Mountain View, CA) gained FDA-approval [3]. In the same year, a French team used the Da Vinci to perform the world's first robotic radical prostatectomy [4]. Robotic surgery has several advantages to the normal laparoscopic approach. It provides a three-dimensional visual field with depth perception. Its 'wristed' instruments provide the natural seven degrees of motional freedom mimicking open surgery, and tremor is eliminated. The ergonomics of the surgeon at the robotic console is improved compared to laparoscopic operating. These advances increase dexterity, improve hand-eye coordination, and reduce surgeon fatigue, which may extend the capabilities of the surgeon, in cases thought to be unfeasible laparoscopically. Using a robotic approach, hand dominance is eliminated during surgical tasks [5], and the visual benefit of 3D optics, reduces distraction level compared to 2D surgery allowing for better focus [6]. Even when comparing 3D robotic and 3D laparoscopic operating, the robotic group perform tasks with less errors [7]. These advantages enable precise positioning of instruments and a relative ease of suturing, which may be advantageous when dealing with small vessels, and difficult anastomoses, particularly important in pancreatic surgery. In addition, as the surgeon controls the camera position and all instruments, the reliance on the skills of the surgical assistant is reduced. Further, we have shown that the learning curve to acquire surgical skills is significantly shorter after robotic, compared to laparoscopic, training (unpublished data). Robotic surgery is gaining momentum in many surgical specialties including urology, colorectal surgery, cardiothoracics, neuro-surgery, gynaecology and endocrine surgery [8–12]. Certainly, robotic surgery has transformed radical prostatectomy (PT) to the point that open surgery is performed in only 12% of cases in the UK [13] whilst laparoscopic PT never gained popularity amongst urologists due to technical difficulties. Giulianotti performed the first successful robotic PD in 2003 demonstrating that robotic pancreatic surgery provides the benefits of minimally invasive surgery whilst bypassing the disadvantages associated with laparoscopic surgery [14, 15]. Since this time there has been a growing body of observational studies published, demonstrating that robotic pancreatic surgery is feasible and safe.

To date however, there are several disadvantages of using a robotic approach for operations. Firstly, the cost of robotic surgery is far higher than laparoscopic techniques. A Da Vinci robotic surgical system costs up to two million US dollars. Further, there are annual maintenance costs, and each instrument can only be used a limited number of times before replacement is necessary. With a rapid improvement in technology, robotic systems are constantly being developed, which may therefore necessitate regular updates by hospitals. Currently, the robotic system is large and cumbersome, this can be an issue in some smaller and overcrowded operating theatres. There is also a lack of haptic feedback (force and tactile) in robotic surgery, such that all operating must be conducted by vision alone. As robotic pancreatic surgery is a new technology, there is as yet, an absence of robust and established evidence to justify its use despite the perceived advantages. However, many of these problems may well diminish with future developments.

58.2 Techniques in Robotic Pancreatic Surgery

A major advantage of robotic surgery is to allow the standardisation of techniques in pancreatic cancer surgery, and to enable video analysis and assessment of operations.

58.2.1 Pancreaticoduodenectomy (PD)

Procedural steps for robotic PD have been published by Giulianotti et al. [16], and is outlined below. There may be some variation in the procedure including: a different order of steps; a combination of established vascular ligation techniques; instruments used for pancreatic transection; preference of suture material for the anastomoses; and pancreatic anastomosis technique.

58.2.1.1 Patient Positioning and Port Insertion (Fig. 58.1a, b)

Patients are positioned in the supine position with at least 15 degrees reverse Trendelenburg and 10–15 degree left-side tilt. The legs are parted with the hips and knees slightly flexed, arms are abducted. The surgical assistant sits or stands between the legs. Pneumoperitoneum is induced either with a Veress needle at Palmer's point or with a subumbilical Hassan technique, which is the authors' preferred method. Standardisation of port placement is recommended, allowing for some variance based on the patient's body conformation. The Si and X system is docked from the head of the patient, whilst the Xi system is docked from the patient's left side. The camera port is positioned in the right para-rectal line, just superior to the umbilicus

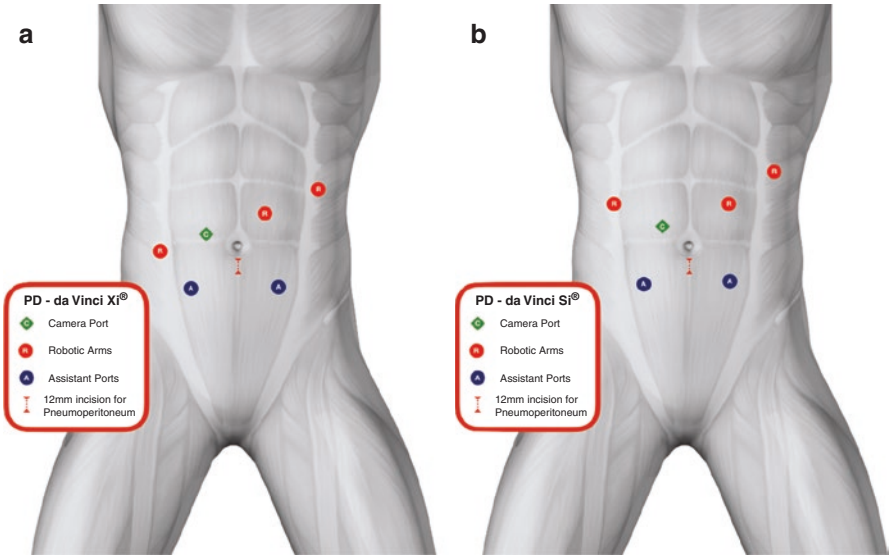

Fig. 58.1 (**a**) Port positioning for pancreaticoduodenectomy using the Da Vinci Xi. (**b**) Port positioning for pancreaticoduodenectomy using the Da Vinci Si

as camera arm or arm 2. One robotic arm is positioned to the right of the camera port as arm 1, and two to the left of the camera port as arms 3 and 4. With the X and Xi system these ports are placed in a horizontal line, at least 4 cm apart (Fig. 58.1a), with the Si system, the ports are placed in a 'u shape', at least 5–6 cm apart (Fig. 58.1b). Two 10 mm assistant ports are placed at least 5 cm below the line of the robotic ports, between the camera port and the robotic arms to the left, and right of the camera. The authors' preferred initial instrument insertion is bipolar fenestrated forceps in arm 1, hook diathermy in arm 3 and cardiere forceps in arm 4. Arm 3 is where the majority of instrument changes take place, swapping the hook for the vessel sealer, needle holder, hem-o-lok and scissors, as required.

58.2.1.2 Procedural Steps

A laparoscopy is performed, and the operation abandoned if any liver or peritoneal metastases are seen. The gastro-colic ligament is divided up to the short gastric vessels with monopolar diathermy hook and/or vessel sealer, and the lesser sac entered. Inspection for tumour invasion into the posterior gastric wall, small bowel or colonic mesentery is made. The right gastro-epiploic artery is divided with the vessel sealer. The posterior wall of the distal stomach or duodenum is dissected and either a robotic or laparoscopic stapler used to transect the stomach (whipples) or duodenum (pylorus-preserving PD). Dissection of the hepatic hilum is commenced to expose the common, right and left hepatic arteries and the common bile duct. The gastro-duodenal artery (GDA) is dissected and exposed and ligated with a robotic or laparoscopic

stapler (preferably curved-tip) or with ties and hem-o-lok clips. The Kocher manoeuvre is completed up to the left side of the aorta, aided by retraction of the pylorus/duodenal stump with the robotic third arm. The jejunum is then divided at 5–10 cm distal to the Treitz ligament with a robotic or laparoscopic stapler below the mesocolon. A retrograde cholecystectomy is performed to the cystic duct and the common bile duct is dissected from the portal vein and transected with monopolar diathermy or with scissors. A tunnel is then created under the pancreas, anterior to the portal vein. The pancreas is divided with an energy device (vessel sealer, monopolar diathermy or harmonic). The uncinate process is then mobilised using the vessel sealer and hook. Larger vessels are ligated with ties and/or hem-o-loks. The specimen is extracted in a 15 mm endocatch via a pfannenstiel or sub-umbilical incision. The jejunal loop is passed retrocolic, where possible, into the upper abdomen. A pancreatico-jejunostomy is performed using an end-to-side duct-to-mucosa technique with PDS 4/0 or 5/0 sutures. A small internal stent may be placed into the pancreatic duct. A Blumgart technique may be used to further anchor the pancreas to the jejunum. A pancreatico-gastrostomy with an invagination technique may be performed if the pancreas is soft without a visible pancreatic duct (Robotic PG for normal pancreas with non-visible PD following robotic Whipple's -Pulling Technique, YouTube, Professor Long R Jiao). The hepatico-jejunostomy is then performed using PDS 3/0, 4/0 or 5/0 sutures depending on the size of the duct. A small internal stent may be placed into the hepatic duct. A gastro/duodeno-jejunostomy is created on a loop of jejunum at least 50 cm distally to the biliary anastomosis using a robotic or laparoscopic stapler. A jejuno-jejunostomy may then be performed with a stapler at least 10 cm proximal to the gastro-jejunostomy to aid biliary drainage. Two Robinsons drains (20 Fr) are placed, one by the pancreatico-jejunostomy and one by the hepatico-jejunostomy.

58.2.2 Distal Pancreatectomy (DP)

58.2.2.1 Patient Positioning and Port Insertion (Fig. 58.2a, b)

For body/distal tail of pancreas lesions, patients are positioned in the supine position with at least 15 degrees reverse Trendelenburg, this positioning aids dissection of the pancreas from the portal vein. For proximal tail of pancreas lesions, we advocate a right lateral decubitas position similar to that used for adrenalectomy to allow easier dissection of the splenic hilum and mobilisation of the spleen. The legs are parted with the hips and knees slightly flexed, arms are abducted. The surgical assistant sits or stands between the legs. Pneumoperitoneum is induced either with a Veress needle at Palmer's point or with a subumbilical hassan technique, which is the authors' preferred method. In the supine position, the ports are placed as outlined in Fig. 58.2. In the right lateral position, the port position may vary in relation to the patient's anatomy, but in general the ports are placed in a horizontal line (Xi) or u-shape (Si), with the centre, to the right and superior to the umbilicus. An assistant 10 mm port is placed 5 cm inferior to the robotic port line. Instrument insertion is as for DP.

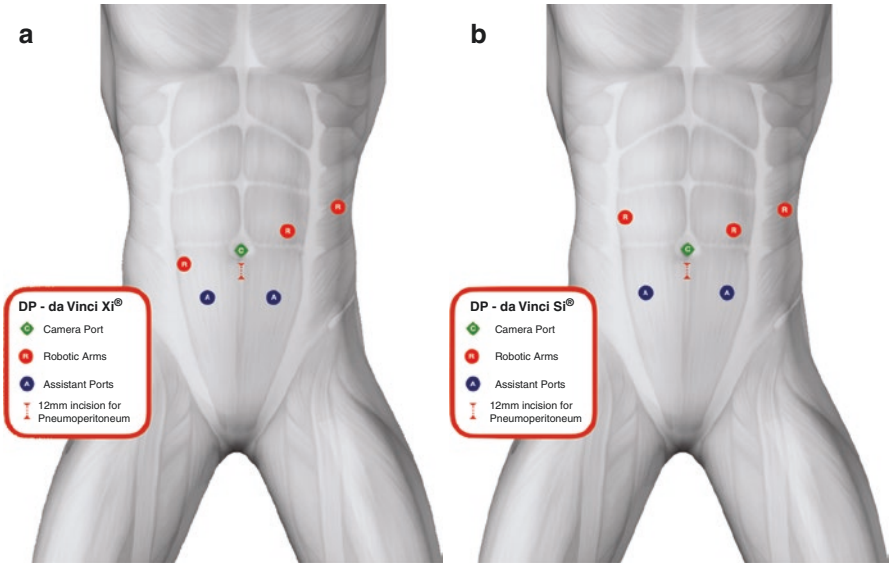

Fig. 58.2 (**a**) Port positioning for distal pancreatectomy using the Da Vinci Xi. (**b**) Port positioning for distal pancreatectomy using the Da Vinci Si

58.2.2.2 Procedural Steps

Coratti et al. outlined procedural steps for robotic DP [17]. In brief, the gastrocolic ligament is divided with the hook and/or vessel sealer up to the gastrolienal ligament. The short gastric vessels may be divided with the vessel sealer and/or hem-o-lok clips. The stomach is retracted with the cardiere forceps and the transverse colon and splenic flexure mobilised. The inferior edge of the pancreas is identified and, at the site chosen for pancreatic transection, a plane is developed behind the pancreas. Two suspension PDS sutures are placed to aid pancreatic retraction. If the transection plane is at the pancreatic neck, then the splenic artery and vein are identified separately and ligated with hem-o-loks. If the transection plane is left of the coeliac trunk, then the splenic artery and vein may be ligated and divided en-bloc with the pancreatic parenchyma. We use an endo-GIA or robotic stapler to transect the pancreatic parenchyma. The proximal pancreatic stump is retracted superiorly to aid a retropancreatic avascular plane of dissection up to the splenic hilum. The spleen is then mobilised aided by retraction of the spleen to the right, allowing transection of the splenorenal ligament with the hook or vessel sealer. The specimen is removed in an endocatch via a pfannenstiel or subumbilical incision (supine position) or a left lateral incision (right lateral decubitas position). A 20 Fr Robinsons drain is placed to cover drainage of the pancreatic stump and splenic bed.

58.3 Outcomes for Robotic Pancreatic Surgery

A systematic MEDLINE search was conducted including only series with >25 clinical cases. Prior to 2010 there were no reported series for robotic pancreatic resections. Currently, there are no randomised controlled trials analysing robotic versus open or laparoscopic PD or DP. For each study details on patient demographics, operative outcomes and oncological information were recorded using a pre-set data extraction form. Data was tabulated and analysed for the means and standard deviations for each variable.

58.3.1 Pancreaticoduodenectomy (PD)

In the published literature, there are 11 reported series of at least 25 robotic PD cases since 2010 with 576 combined cases [14, 18–26]. Outcomes are promising and summarised in Tables 58.1 and 58.2.

Table 58.1 Operative details for robotic pancreaticoduodenectomy (PD)

Publication			Operative details					
Series	Country	Year	Number of cases	Patient age (mean, years)	Operative time (mean, min)	EBL (mean, ml)	Transfusion rate (%)	Conversion to open (%)
Giulianotti et al.	USA and Italy	2010	60	58	421	394	10.00	18.30
Buchs et al.	IL, USA	2011	44	63	444	387	22.70	4.50
Chalikonda et al.	OH, USA	2012	30	62	476	485	NR	10.00
Zeh et al.	Pa, USA	2012	50	68	568	350	22.00	16.00
Boggi et al.	Italy	2013	34	60	597	220	2.90	0.00
Zureikat et al.	PA, USA	2013	132	65	527	300	11.00	8.00
Napoli et al.	Italy	2016	112	60	526.3	NR	28.60	2.70
Coratti et al.	Italy	2016	36	67	510	150	NR	22.20
Liu et al.	China	2016	27	57	387	219	NR	0.00
Marino et al.	Italy	2018	26	62	540	290	7.70	15.30
Gall et al.	UK	2019	25	61	452	109	0.00	0.00
Pooled analysis			576	62.09 ± 3.48	495.3 ± 64.76	290.4 ± 117.50	13.11 ± 9.56	8.82 ± 7.71

Key: *NR* not recorded, *EBL* estimated blood loss

Table 58.2 Outcomes for robotic pancreaticoduodenectomy (PD)

Publication			Post-operative details				Oncological details			
Series	Country	Year	LOS (mean, days)	Morbidity rate, Clavien Dindo ≥3 (%)	Pancreatic fistula (%)	90 Day mortality (%)	Malignant cases (%)	T size (mean, mm)	Number of lymph nodes harvested (mean)	R0 resection margin (%)
Giulianotti et al.	USA and Italy	2010	22.00	26.00	31.30	0.00	75.00	29.00	17.50	91.70
Buchs et al.	IL, USA	2011	13.00	36.40	18.20	4.50	75.00	NR	16.80	93.20
Chalikonda et al.	OH, USA	2012	9.79	30.00	6.00	4.00	46.67	30.00	13.20	100.00
Zeh et al.	Pa, USA	2012	10.00	30.00	22.00	2.90	74.00	27.00	18.00	89.00
Boggi et al.	Italy	2013	23.00	15.00	38.20	2.90	58.82	NR	32.00	100.00
Zureikat et al.	PA, USA	2013	10.00	21.20	17.00	3.80	80.00	NR	19.00	87.70
Napoli et al.	Italy	2016	22.00	19.60	33.00	3.60	58.04	NR	47.00	75.80
Coratti et al.	Italy	2016	9.00	33.30	16.60	5.50	88.89	NR	29.80	93.70
Liu et al.	China	2016	17.00	29.60	14.80	3.70	85.19	22.40	8.00	100.00
Marino et al.	Italy	2018	13.00	15.40	19.20	3.90	80.77	22.00	28.00	90.50
Gall et al.	UK	2019	13.80	20.00	8.00	4.00	80.00	23.30	17.88	60.00
Pooled analysis			14.78 ± 5.37	25.14 ± 6.95	20.39 ± 9.64	3.45 ± 1.37		25.62 ± 3.50	22.47 ± 10.37	89.24 ± 11.95

Key: *N*R not recorded, *LOS* length of hospital stay

A pooled analysis found a **mean operative time** of 495.3 ± −64.8 min (range 387–597 min) with a combined conversion rate of only 8.82 ± 7.71%. Some series comparing robotic and open PD report a longer mean operating time for robotic PD [27] however, a meta-analysis of robotic PD versus open PD comparative studies analysing 680 patients, did not find a significant difference in operating time [28]. Further, minimally invasive procedures do not result in a peri-operative cortisol peak compared to a cortisol surge in open surgery, irrespective of procedure duration [29, 30]. Therefore, despite potentially longer operating times, there is likely a reduced surgical stress response in robotic compared to open PD. The **conversion rate** to open operation (n = 37) is also significantly less for robotic (n = 25) than laparoscopic PD (n = 41) (Gall et al. unpublished data), highlighting the increased difficulty with laparoscopic techniques. The **mean estimated blood loss** (EBL) was 290.4 ± 117.50 with no series reporting a mean blood loss more than the clinically significant 500mls. Indeed, only 13.11 ± 9.56% of patients required perioperative blood transfusion. This is consistently reported as a major advantage for minimally invasive PD [31].

The mean **length of post-operative stay** was 14.78 ± 5.37 days. An improvement in length of stay for robotic compared to open PD has been observed in three meta-analyses [27, 28, 32], and may also be shorter compared to laparoscopic PD (Gall et al. unpublished data). Serious **morbidity** was recorded in 21.14 ± 6.95% with post-operative pancreatic fistula in 20.39 ± 9.64%. **90-day mortality** amongst all series was 3.45 ± 1.37%. Meta-analyses of comparative case series show no significant difference in morbidity and mortality between robotic and open PD [14, 18, 22].

Pooled analysis of oncological details revealed an **R0 resection rate** of 89.24 ± 11.95%, although this high rate may be due to the selection of smaller tumours (mean tumour size was 25.62 ± 3.50 mm). The average number of **harvested lymph nodes** across all series was 22.47 ± 10.37, more than the 15, recommended by The European society for medical oncology (ESMO) [33].

58.3.2 Distal Pancreatectomy (DP)

There are 11 reported series of at least 25 DP cases with a total of 872 cases [22, 34–43] (outcomes and pooled analysis summarised in Tables 58.3 and 58.4). Only 31.50 ± 23.42% of these were for pancreatic ductal adenocarcinoma, the majority undertaken for NETs or benign pathologies. An advantage of robotic DP appears to be a higher spleen preservation rate [44], however, this is obviously not relevant in malignant cases, which mandate splenectomy.

Our pooled analysis showed a **mean operative time** of 223.4 ± 60.6 minutes with an estimated blood loss of 135.5 ± 45.1 and perioperative blood transfusion in 6.2 ± 3.8%. Despite robotic DP having longer operating times than laparoscopic and open resections [45, 46], an improved **estimated blood loss** is consistently reported

Table 58.3 Operative details for robotic distal pancreatectomy (DP)

Publication			Operative details					
Series	Country	Year	Number of cases	Patient age (mean, years)	Operative time (mean, min)	EBL (mean, ml)	Transfusion rate (%)	Conversion to open (%)
Daouadi et al.	USA	2013	30	59.00	293.00	150.00	10.00	0.00
Zureikat et al.	USA	2013	83	65.00	256.00	150.00	11.00	2.00
Lee et al.	USA	2015	37	58.00	213.00	193.00	NR	38.00
Napoli et al.	Italy	2015	55	56.60	278.20	NR	8.30	0.00
Chen et al.	China	2015	69	56.20	150.00	100.00	2.90	0.00
Zhang et al.	China	2017	43	48.70	139.30	50.00	9.30	0.00
Lelpo et al.	Spain	2017	28	59.70	294.00	175.00	NR	3.6
Liu et al.	China	2018	210	48.30	159.80	161.20	4.30	4.80
Marino et al.	Italy	2019	35	59.30	230.00	95.00	0.00	2.9% [1]
Hong et al.	South Korea	2019	46	51.20	166.40	NR	NR	0.00
Alfieri et al.	Italy	2019	236	58.00	277.80	145.00	3.4% [8]	6.3% [15]
Pooled analysis			872	56.36 ± 5.07	223.41 ± 60.63	135.47 ± 45.07	6.15 ± 3.75	5.24 ± 10.58

Key: *NR* not recorded, *EBL* estimated blood loss

in comparative studies of robotic, open and laparoscopic DP [34, 47]. Further, a **conversion rate** of only 5.2 ± 10.6% is consistent with others reporting this to be lower in robotic compared to laparoscopic DP [34, 45].

Total **length of hospital stay** was 8 ± 2.7 days. Indeed, three recent meta-analyses of robotic versus laparoscopic and open DP, all confirmed a shorter length of hospital stay for robotic resections [45–47], resulting in lower total costs for the robotic technique [48]. Although some report a reduced morbidity rate for robotic DP compared to laparoscopic [34] and open [46] techniques, others have found comparable morbidity and mortality [45]. Certainly, this does not appear to be worse in comparative reports. Further, there is no reported difference in terms of oncological outcomes [34]. Indeed, our pooled analysis found an **R0 resection rate** of 98 ± 5.4% with a mean of 14.3 ± 4.3 **lymph nodes** harvested.

These initial results show that, in experienced hands, robotic PD and DP have similar outcomes to open and laparoscopic techniques whilst reducing blood loss, transfusion rate and length of stay. However, in surgeons' early experience, there is likely bias in terms of case selection. Further, the long term oncological outcomes are infrequently reported. The overall quality of evidence however is poor and randomized controlled trials are required to confirm the outcomes.

Table 58.4 Outcomes for robotic distal pancreatectomy (DP)

Publication			Post-operative details				Oncological details			
Series	Country	Year	LOS (mean, days)	Morbidity rate, Clavien Dindo ≥3 (%)	Pancreatic fistula (%)	90 Day mortality (%)	Malignant cases (%)	T size (mean, mm)	Number of lymph nodes harvested (mean)	R0 resection margin (%)
Daouadi et al.	USA	2013	6.00	20.00	46.00	0.00	43.33	31.00	19.00	100
Zureikat et al.	USA	2013	6.00	13.00	43.00	0.00	72.29	NR	14.00	97
Lee et al.	USA	2015	5.00	43.00	8.00	0.00	10.81	NR	12.00	100
Napoli et al.	Italy	2015	12.60	3.60	52.70	0.00	7.27	NR	16.00	100
Chen et al.	China	2015	11.60	8.00	24.60	0.00	23.12	40.00	15.50	100
Zhang et al.	China	2017	12.80	25.60	25.60	0.00	0.00	16.00	3.50	100
Lelpo et al.	Spain	2017	8.90	7.10	10.70	0.00	53.57	35.40	14.20	100
Liu et al.	China	2018	8.50	6.70	14.30	0.00	34.76	25.00	NR	NR
Marino et al.	Italy	2019	9.20	5.70	17.10	2.90	60.00	32.00	14.40	100
Hong et al.	South Korea	2019	8.00	2.20	47.80	0.00	26.09	34.10	17.90	83
Alfieri et al.	Italy	2019	10.20	13.80	36.00	0.80	15.25	NR	16.20	100
Pooled analysis			8.98 ± 2.66	13.52 ± 11.53	29.62 ± 15.40	0.34 ± 0.84	31.50 ± 23.42	30.50 ± 7.86	14.27 ± 4.28	98 ± 5.35

Key: *NR* not recorded, *LOS* length of hospital stay

58.4 The Future of Robotic Pancreatic Surgery

We anticipate that HPB will advance into minimally invasive approaches and robotic solutions will become more attractive, particularly given the precision of robotic instruments, and the improved ergonomics, both important considerations in pancreatic surgery as supported by the International Robotic hepatopancreaticobiliary Focus group, held at the IHPBA meeting in Geneva in September 2018. The major disadvantage to robotics is cost. Limiting robotic HPB surgery to high volume centres combined with other surgical robotic specialties can also offset costs, as has been shown in rectal surgery [49]. We envisage that technological advances will continue over the coming decades, leading to the introduction of haptic feedback, artificial intelligence, a reduction in overall system size, and improved speed of instrument changes, which will add further benefit to the robot. The public perception of robotic surgery is of perceived benefit, and certainly there is a preference for minimally invasive surgery [50]. Patient demand may become the driving force for the future establishment of robotics in HPB. It is paramount that trainees develop robotic skills, with the majority of current trainees believing that a formal robotic surgical curriculum should be established, and exposure should begin in year one of surgical training [51].

58.5 Conclusion

Robotic pancreatic surgery offers major advantages over open and laparoscopic surgery. It is the future of pancreatic surgery if platform is readily available to HPB surgeons with a reduced cost.

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References

1. Wang M, Peng B, Liu J, Yin X, Tan Z, Liu R, et al. Practice patterns and perioperative outcomes of laparoscopic pancreaticoduodenectomy in China: a retrospective multicenter analysis of 1029 patients. Ann Surg. 2021;273(1):145–53.
2. van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol Hepatol. 2019;4(3):199–207.
3. Yates DR, Vaessen C, Roupret M. From Leonardo to Da Vinci: the history of robot-assisted surgery in urology. BJU Int. 2011;108(11):1708–13; discussion 14.
4. Abbou CC, Salomon L, Hoznek A, Antiphon P, Cicco A, Saint F, et al. Laparoscopic radical prostatectomy: preliminary results. Urology. 2000;55(5):630–4.

5. Badalato GM, Shapiro E, Rothberg MB, Bergman A, RoyChoudhury A, Korets R, et al. The Da Vinci robot system eliminates multispecialty surgical trainees' hand dominance in open and robotic surgical settings. J Soc Laparoendosc Surg. 2014;18(3):e2014.
6. Kim S, May A, Ryan H, Mohsin A, Tsuda S. Distraction and proficiency in laparoscopy: 2D versus robotic console 3D immersion. Surg Endosc. 2017;31(11):4625–30.
7. Shakir F, Jan H, Kent A. 3D straight-stick laparoscopy versus 3D robotics for task performance in novice surgeons: a randomised crossover trial. Surg Endosc. 2016;30(12):5380–7.
8. Yu HY, Hevelone ND, Lipsitz SR, Kowalczyk KJ, Hu JC. Use, costs and comparative effectiveness of robotic assisted, laparoscopic and open urological surgery. J Urol. 2012;187(4):1392–8.
9. Midura EF, Hanseman DJ, Hoehn RS, Davis BR, Abbott DE, Shah SA, et al. The effect of surgical approach on short-term oncologic outcomes in rectal cancer surgery. Surgery. 2015;158(2):453–9.
10. Cheng CL, Rezac C. The role of robotics in colorectal surgery. Br Med J. 2018;360:j5304.
11. Chitwood WR Jr. Robotic cardiac surgery by 2031. Tex Heart Inst J. 2011;38(6):691–3.
12. Diodato MD Jr, Damiano RJ Jr. Robotic cardiac surgery: overview. Surg Clin North Am. 2003;83(6):1351–67, ix.
13. Khadhouri S, Miller C, Fowler S, Hounsome L, McNeill A, Adshead J, et al. The British Association of Urological Surgeons (BAUS) radical prostatectomy audit 2014/2015—an update on current practice and outcomes by Centre and surgeon case-volume. BJU Int. 2018;121(6):886–92.
14. Giulianotti PC, Sbrana F, Bianco FM, Elli EF, Shah G, Addeo P, et al. Robot-assisted laparoscopic pancreatic surgery: single-surgeon experience. Surg Endosc. 2010;24(7):1646–57.
15. Hanly EJ, Talamini MA. Robotic abdominal surgery. Am J Surg. 2004;188(4A Suppl):19s–26s.
16. Giulianotti PC, Mangano A, Bustos RE, Gheza F, Fernandes E, Masrur MA, et al. Operative technique in robotic pancreaticoduodenectomy (RPD) at University of Illinois at Chicago (UIC): 17 steps standardized technique : lessons learned since the first worldwide RPD performed in the year 2001. Surg Endosc. 2018;32(10):4329–36.
17. Parisi A, Coratti F, Cirocchi R, Grassi V, Desiderio J, Farinacci F, et al. Robotic distal pancreatectomy with or without preservation of spleen: a technical note. World J Surg Oncol. 2014;12:295.
18. Buchs NC, Addeo P, Bianco FM, Ayloo S, Benedetti E, Giulianotti PC. Robotic versus open pancreaticoduodenectomy: a comparative study at a single institution. World J Surg. 2011;35(12):2739–46.
19. Chalikonda S, Aguilar-Saavedra JR, Walsh RM. Laparoscopic robotic-assisted pancreaticoduodenectomy: a case-matched comparison with open resection. Surg Endosc. 2012;26(9):2397–402.
20. Zeh HJ, Zureikat AH, Secrest A, Dauoudi M, Bartlett D, Moser AJ. Outcomes after robot-assisted pancreaticoduodenectomy for periampullary lesions. Ann Surg Oncol. 2012;19(3):864–70.
21. Boggi U, Signori S, De Lio N, Perrone VG, Vistoli F, Belluomini M, et al. Feasibility of robotic pancreaticoduodenectomy. Br J Surg. 2013;100(7):917–25.
22. Zureikat AH, Moser AJ, Boone BA, Bartlett DL, Zenati M, Zeh HJ 3rd. 250 robotic pancreatic resections: safety and feasibility. Ann Surg. 2013;258(4):554–9; discussion 9–62.
23. Napoli N, Kauffmann EF, Menonna F, Perrone VG, Brozzetti S, Boggi U. Indications, technique, and results of robotic pancreatoduodenectomy. Updates Surg. 2016;68(3):295–305.
24. Coratti A, Di Marino M, Coratti F, Baldoni G, Guerra F, Amore Bonapasta S, et al. Initial experience with robotic pancreatic surgery: technical feasibility and oncological implications. Surg Laparosc Endosc Percutan Tech. 2016;26(1):31–7.
25. Liu R, Zhang T, Zhao ZM, Tan XL, Zhao GD, Zhang X, et al. The surgical outcomes of robot-assisted laparoscopic pancreaticoduodenectomy versus laparoscopic pancreaticoduodenectomy for periampullary neoplasms: a comparative study of a single center. Surg Endosc. 2017;31(6):2380–6.
26. Marino MV, Shabat G, Potapov O, Gulotta G, Komorowski AL. Robotic pancreatic surgery: old concerns, new perspectives. Acta Chir Belg. 2019;119(1):16–23.

27. Zhao W, Liu C, Li S, Geng D, Feng Y, Sun M. Safety and efficacy for robot-assisted versus open pancreaticoduodenectomy and distal pancreatectomy: a systematic review and meta-analysis. Surg Oncol. 2018;27(3):468–78.
28. Peng L, Lin S, Li Y, Xiao W. Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy. Surg Endosc. 2017;31(8):3085–97.
29. Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, et al. Redefining the stress cortisol response to surgery. Clin Endocrinol (Oxf). 2017;87(5):451–8.
30. Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, et al. The cortisol stress response induced by surgery: a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018;89(5):554–67.
31. Pedziwiatr M, Malczak P, Pisarska M, Major P, Wysocki M, Stefura T, et al. Minimally invasive versus open pancreatoduodenectomy—systematic review and meta-analysis. Langenbecks Arch Surg. 2017;402(5):841–51.
32. Shin SH, Kim YJ, Song KB, Kim SR, Hwang DW, Lee JH, et al. Totally laparoscopic or robot-assisted pancreaticoduodenectomy versus open surgery for periampullary neoplasms: separate systematic reviews and meta-analyses. Surg Endosc. 2017;31(9):3459–74.
33. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
34. Marino MV, Mirabella A, Gomez Ruiz M, Komorowski AL. Robotic-assisted versus laparoscopic distal pancreatectomy: the results of a case-matched analysis from a tertiary care center. Dig Surg. 2019;37:229–39.
35. Daouadi M, Zureikat AH, Zenati MS, Choudry H, Tsung A, Bartlett DL, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. Ann Surg. 2013;257(1):128–32.
36. Lee SY, Allen PJ, Sadot E, D'Angelica MI, DeMatteo RP, Fong Y, et al. Distal pancreatectomy: a single institution's experience in open, laparoscopic, and robotic approaches. J Am Coll Surg. 2015;220(1):18–27.
37. Napoli N, Kauffmann EF, Perrone VG, Miccoli M, Brozzetti S, Boggi U. The learning curve in robotic distal pancreatectomy. Updates Surg. 2015;67(3):257–64.
38. Chen S, Zhan Q, Chen JZ, Jin JB, Deng XX, Chen H, et al. Robotic approach improves spleen-preserving rate and shortens postoperative hospital stay of laparoscopic distal pancreatectomy: a matched cohort study. Surg Endosc. 2015;29(12):3507–18.
39. Zhang J, Jin J, Chen S, Gu J, Zhu Y, Qin K, et al. Minimally invasive distal pancreatectomy for PNETs: laparoscopic or robotic approach? Oncotarget. 2017;8(20):33872–83.
40. Ielpo B, Duran H, Diaz E, Fabra I, Caruso R, Malave L, et al. Robotic versus laparoscopic distal pancreatectomy: a comparative study of clinical outcomes and costs analysis. Int J Surg. 2017;48:300–4.
41. Liu R, Liu Q, Zhao ZM, Tan XL, Gao YX, Zhao GD. Robotic versus laparoscopic distal pancreatectomy: a propensity score-matched study. J Surg Oncol. 2017;116(4):461–9.
42. Hong S, Song KB, Madkhali AA, Hwang K, Yoo D, Lee JW, et al. Robotic versus laparoscopic distal pancreatectomy for left-sided pancreatic tumors: a single surgeon's experience of 228 consecutive cases. Surg Endosc. 2020;34(6):2465–73.
43. Alfieri S, Boggi U, Butturini G, Pietrabissa A, Morelli L, Di Sebastiano P, et al. Full robotic distal pancreatectomy: safety and feasibility analysis of a multicenter cohort of 236 patients. Surg Innov. 2020;27(1):11–8.
44. Alfieri S, Butturini G, Boggi U, Pietrabissa A, Morelli L, Vistoli F, et al. Short-term and long-term outcomes after robot-assisted versus laparoscopic distal pancreatectomy for pancreatic neuroendocrine tumors (pNETs): a multicenter comparative study. Langenbecks Arch Surg. 2019;404(4):459–68.
45. Kamarajah SK, Sutandi N, Robinson SR, French JJ, White SA. Robotic versus conventional laparoscopic distal pancreatic resection: a systematic review and meta-analysis. HPB (Oxford). 2019;21:1107–18.

46. Niu X, Yu B, Yao L, Tian J, Guo T, Ma S, et al. Comparison of surgical outcomes of robot-assisted laparoscopic distal pancreatectomy versus laparoscopic and open resections: a systematic review and meta-analysis. Asian J Surg. 2019;42(1):32–45.
47. Gavriilidis P, Roberts KJ, Sutcliffe RP. Comparison of robotic vs laparoscopic vs open distal pancreatectomy. A systematic review and network meta-analysis. HPB (Oxford). 2019;21(10):1268–76.
48. Magge DR, Zenati MS, Hamad A, Rieser C, Zureikat AH, Zeh HJ, et al. Comprehensive comparative analysis of cost-effectiveness and perioperative outcomes between open, laparoscopic, and robotic distal pancreatectomy. HPB (Oxford). 2018;20(12):1172–80.
49. Hottenrott C. Robotic versus laparoscopic surgery for rectal cancer and cost-effectiveness analysis. Surg Endosc. 2011;25(12):3954–6; author reply 7–8.
50. Boys JA, Alicuben ET, DeMeester MJ, Worrell SG, Oh DS, Hagen JA, et al. Public perceptions on robotic surgery, hospitals with robots, and surgeons that use them. Surg Endosc. 2016;30(4):1310–6.
51. George LC, O'Neill R, Merchant AM. Residency training in robotic general surgery: a survey of program directors. Minim Invasive Surg. 2018;2018:8464298.

Chapter 59
Robotic-Assisted Pancreatic Surgery for Pancreatic Cancer: Technical Aspects

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Take Home Messages

- Appropriate patient selection, especially in the early phase of a robotic pancreas program, is paramount to achieve optimal outcomes.
- Adequate training, close coaching and the use of two-faculty approach is necessary to build a successful program.
- Published data on the safety, feasibility and oncologic outcomes mainly emanates from high volume centers. Therefore, cautious use and interpretation of these data is advisable when starting a program.

Pearls and Pitfalls

- Expertise in both pancreatic and robotic surgery is needed to establish a successful robotic program.
- Conversion to open surgery in the setting of hemorrhage should be prompt and requires impeccable coordination between operating surgeons and operating room staff. Injury to the portal vein and its tributary system can often be controlled by compression of the vessel with a laparoscopic instrument and a gauze. This maneuver permits to undock the robotic platform in a controlled fashion and to gain undisturbed access to the abdomen for a laparotomy.

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Future Perspectives
- Randomized trials are needed to ascertain the safety and oncologic efficacy of robotic pancreatic surgery in comparison to the open approach.

59.1 Introduction

The use of robotic surgery has been widely adopted in many surgical procedures but its application in pancreatic resection for cancer has lagged due to the complexity of the operation, the high morbidity of the surgery and the concern of inferior oncologic outcomes (Table 59.1). Over the last decade, multiple studies showed that robotic pancreatic surgery is safe, feasible, and has at least equivalent morbidity profile and oncologic outcomes compared to open surgery [1–14].

In 2019, the Miami international evidence-based guidelines on minimally invasive pancreas resection were published and supported the use of minimally invasive distal pancreatectomy for pancreatic ductal adenocarcinoma and low-grade malignant tumors but acknowledged that there is insufficient data to recommend minimally invasive pancreaticoduodenectomy (PD) over the open approach [15].

In our institution, we created a program to optimize the robotic approach for PD starting 2008. First, we focused on understanding the safety and feasibility of the procedure. This was followed by studies on the optimal learning curve which is

Table 59.1 Outcomes Table comparing RPD to OPD/LPD and RDP to ODP/LDP

Author	Year	Approach	Number	Mortality (%)	Major morbidity (%)	LOS (days)	OT (min)
Zureikat et al. [6]	2016	RPD vs. OPD	211 vs. 817	1.9 vs. 2.8[b]	23 vs. 23	8 vs. 8[a]	402 vs. 300[c]
Kowalsky et al. [1]	2019	RPD vs. OPD	159 vs. 95	4 vs. 6[b]	26 vs. 33	7 vs. 8[a]	371 vs. 413[c]
Nassour et al. [14]	2017	RPD vs. LPD	193 vs. 235	1 vs. 2.6	55 vs. 49	11 vs. 11	422 vs. 429
Nassour et al. [11]	2017	RPD vs. LPD	165 vs. 1458	4.8 vs. 5.6[b]		9 vs. 8[a]	
Lee et al. [16]	2014	RDP vs. ODP	37 vs. 637	0 vs. 0.6[b]	43 vs. 25	5 vs. 7[a]	213 vs. 185[c]
Magge et al. [2]	2018	RDP vs. ODP	196 vs. 85	0 vs. 3.5[c]	14 vs. 21	6 vs. 8[a]	211 vs. 316[c]
Daouadi et al. [10]	2013	RDP vs. LDP	30 vs. 94	0 vs. 1.1[b]	20 vs. 14	6 vs. 7	293 vs. 372[c]
Raoof et al. [17]	2018	RDP vs. LDP	99 vs. 605	0 vs. 3[b]		5 vs. 6[a]	

RPD robotic pancreaticoduodenectomy, *OPD* open pancreaticoduodenectomy, *LPD* laparoscopic pancreaticoduodenectomy, *RDP* robotic distal pancreatectomy, *ODP* open distal pancreatectomy, *LDP* laparoscopic distal pancreatectomy, *LOS* length of stay, *OT* operative time

[a]Median Length of Stay (LOS). Otherwise, the values represent mean LOS

[b]90 days mortality. Otherwise, the values represent 30-day mortality

[c]$P < 0.05$

estimated at 80 cases for novice adopters and then we performed multiple comparative studies which supported the efficacy of the robotic approach. Finally, we developed a training program that allows safe propagation of this technique.

In this chapter, we will focus on the technical aspects of robotic pancreaticoduodenectomy (RPD) and distal pancreatectomy (RDP) with or without en bloc resection of the celiac axis.

59.2 Patient Selection for Robotic Pancreatic Surgery

The indication for robotic pancreatic surgery is similar to open approach with few exceptions. Selecting patients adequately, especially in the early learning curve is important to the success of the procedure. Here are key considerations:

(a) Optimal pathology to undergo RPD is small pancreatic adenocarcinoma with pancreatic and biliary duct obstruction. The large size of the ducts and firm texture of the pancreas allow easier reconstruction for novice. Once the surgeon becomes more experienced, the application of this approach may be expanded to other periampullary malignancies.
(b) All patients need high quality triphasic computed tomography scan to determine the relationship of the tumor to the vasculature. Patients who require vascular reconstruction should not undergo robotic surgery—at least for the time being.
(c) Patients with biopsy proven pancreatic body/tail tumor with involvement of any branches of the celiac axis should have a disease-free hepatic trunk and gastroduodenal artery (GDA) to be able to perform a distal pancreatectomy with en bloc resection of the celiac axis.
(d) Patients with extreme BMI (i.e. $\geq$40 or $\leq$20) should not be offered robotic surgery: Patient with low BMI or with small transverse diameter will not have adequate working space for the robotic instruments. On the other hand, patients with high BMI pose a challenge in the mobilization of the transverse mesocolon and the division of the ligament of Treitz from the right upper quadrant.
(e) Since the robotic approach usually takes longer time than the open one, a patient who underwent previous abdominal surgery and has extensive adhesions requiring significant lysis should only rarely if ever be selected for this approach. In addition, a patient with upper gastrointestinal reconstructions should be avoided due to the difficulty of small bowel orientation robotically and the concern of small bowel injury during excessive manipulation due to lack of haptic feedback.

59.3 Robotic Pancreaticoduodenectomy

The patient is positioned on the split-leg table with the legs abducted to allow for the assistant to stand in between the legs. The right arm is tucked, and the left arm is placed on an arm board. The operative table is placed in steep Trendelenburg and rotated 45° away from the anesthesia-related space to allow for the Da Vinci® Si robot to be docked at the head of the table. If the Xi is used, the robot can be docked from the side of the patient.

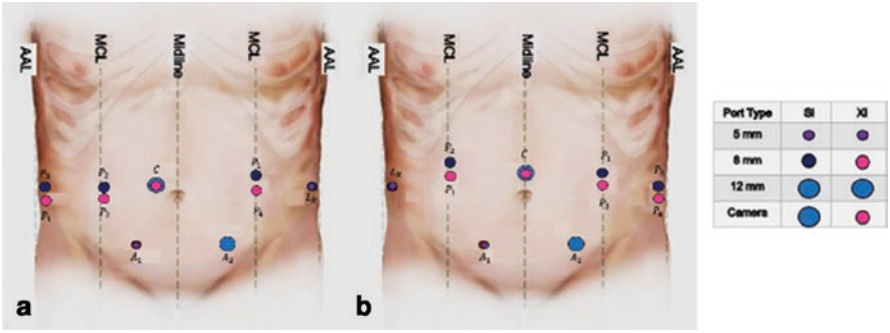

Fig. 59.1 Trocar placement for (**a**) Whipple. (**b**) Distal pancreatectomy

The abdomen is accessed via an incision in the left upper quadrant along the midclavicular line and 3 cm above the umbilicus using a 5 mm zero-degree scope and an optical separator trocar. After insufflation to 15 mmHg, a diagnostic laparoscopy is performed to rule out metastasis and then 6 additional ports are placed as described per Fig. 59.1a. Briefly, the camera 12 mm laparoscopic port is placed 3 cm above and to the right of the umbilicus (note that a 12 mm camera port applies to the DaVinci Si platform only, all Xi ports- including the camera port- are 8 mm). Two 8 mm robotic trocars are placed in the right abdomen in the mid-clavicular (P2) and anterior axillary (P3) line at the same level as the camera. Then, the optical separator–which was used to access the abdomen– is changed to an 8 mm robotic trocar (P1). A 5-mm assistant port is placed a handbreadth below and between the camera and P2, and another 12-mm assistant port is placed a handbreadth below and between the camera and P1. The last 5-mm trocar—through which the Mediflex liver retractor is introduced—is placed laterally just inferior to the left costal margin.

After docking the robot, the resection portion of the operation— which consists of 4 major steps— starts (see Video 59.1).

59.3.1 Right Colon Mobilization, Kocherization and Division of the Ligament of Treitz

Using the hook cautery and the fenestrated bipolar, the gastro-colic ligament is taken down to access the lesser sac inferior to the right gastroepiploic vessels. The stomach is retracted anteriorly with a Prograsp through P3 and all adhesions between the stomach and the pancreatic capsule are taken down. The transverse mesocolon is dissected inferiorly, then the hepatic flexure and right colon are mobilized to expose the duodenum. After kocherization, the ligament of Treitz is divided from the patient's right side and the duodenum is completely freed up allowing for the proximal jejunum to be delivered in the right supracolic compartment. The proximal jejunum is transected 10 cm from the duodenum with a GIA

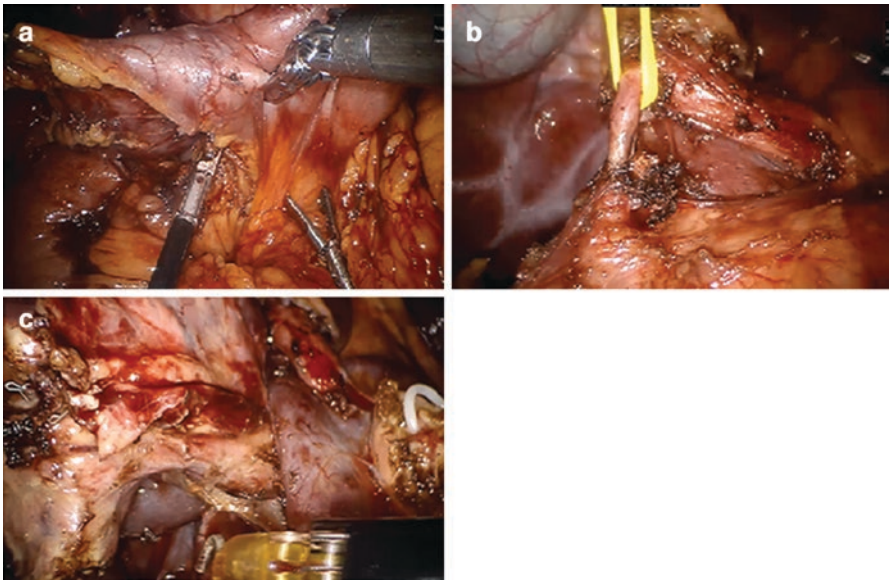

Fig. 59.2 (**a**) After kocherization, the ligament of Treitz is divided, and the jejunum is delivered into the right upper quadrant allowing to linearize the duodenum. (**b**) Dissected GDA. (**c**) Exposed SMV/PV after transection of the pancreas

stapler using a 60 mm gold staple load. The mesentery is divided with the Ligasure™ up to the uncinate process, therefore creating a linearized segment of duodenum (Fig. 59.2a).

59.3.2 Dissection of the Porta-Hepatis

The gastrohepatic ligament is divided with care taken not to injure a replaced or accessory left hepatic artery. Then the stomach is divided with a GIA stapler using a 60 mm purple load exposing the porta hepatis. The station 8A lymph node is dissected off the common hepatic artery and the right gastric artery is doubly clipped with a 5-mm Endo Clip and divided. Using a no touch technique, we dissect the common hepatic artery (CHA), gastroduodenal artery (GDA) and the portal vein (PV). The GDA is circumferentially dissected and transected with a GIA stapler using a 45-mm gold load after confirming that there is still pulse in the hepatic artery when the GDA is clamped (Fig. 59.2b). Then, the common bile duct is dissected circumferentially and off the PV using the robotic monopolar hook cautery and is transected with a GIA stapler with angled tip using a 45 mm gold load to avoid bile spillage. Finally, we dissect along the anterior border of the PV heading inferiorly toward the neck of the pancreas to facilitate creating the retropancreatic tunnel.

59.3.3 Creation of Retropancreatic Tunnel and Transection of the Pancreas

The duodenum is retracted toward the right upper quadrant (P3) creating tension on the gastroepiploic vein. Attention is now directed to the SMV which must be identified at the infra-pancreatic border–by a combination of gentle brushing and energy dissection—and then dissected along its anterior surface, using the hook cautery. Thus, we identify the right gastroepiploic vein, middle colic vein and the trunk of Henle which is divided using the Ligasure™. Then, the retropancreatic tunnel is developed by elevating the pancreas with the fenestrated bipolar and gently pushing down on the SMV with the hook. The neck of the pancreas is then divided with hot monopolar shears until the duct is encountered. The duct is sharply divided to prevent thermal injury (Fig. 59.2c).

59.3.4 Dissection of the Uncinate

The specimen is retracted laterally (using P3 which holds the inferior stapled edge of the transected D1) to expose the uncinate and the small fibers between the uncinate and the SMV/PV are divided. The vein of Belcher is transected superiorly with the Ligasure™. and the first jejunal vein is preserved inferiorly. Then the dissection is continued along the SMA and the inferior pancreaticoduodenal artery is divided. Finally, the retroperitoneal tissue to the right and behind the SMA is resected with the Ligasure™. After performing a cholecystectomy, the specimen is placed in a 15-mm EndoCatch retrieval bag and removed through the LLQ Incision after extending it to 4 cm. A gel port is placed in the extraction site and pneumoperitoneum is re-established in preparation for the reconstruction phase which consists of 3 additional steps (see Video 59.2).

59.3.5 Pancreaticojejunostomy

A modified Blumgart technique is performed for the pancreaticojejunostomy anastomosis (Fig. 59.3a). The pancreatic neck is dissected off the retroperitoneum and the anterior surface of the splenic vein for 1 cm to allow space for the jejunum to oppose firmly to the pancreas. The jejunum is brought behind the root of the mesentery as a neo-duodenum with the antimesenteric border facing the transected edge of the pancreas. Three horizontal mattress sutures (2-0 silk cut to 20 cm) are placed. We start anteriorly on the surface of the pancreas, full thickness through the gland, then we take a horizontal seromuscular bite of the jejunum and finally we go back through the pancreas from posterior to anterior. A 4- or 5- French stent is placed in the duct to prevent narrowing from the second stitch which is placed around the

pancreatic duct. The sutures are tied and the needles are left to be used for the anterior seromuscular layer. The straddling suture around the pancreatic duct is tied loosely to approximate the posterior pancreatic capsule to the jejunal serosal layer but without exerting any external compression on the pancreatic duct. After tying this suture, the pancreatic stent is completely removed from the pancreatic duct and reinserted to ensure patency of the pancreatic duct.

Next, a duct to mucosa anastomosis is performed. After performing an enterotomy on the antimesenteric border of the jejunum directly facing the pancreatic duct, interrupted 5-0 polydioxanone sutures are placed. Posteriorly, two to three sutures are placed and tied. The stent is placed back in the pancreatic duct and into the jejunum. Then anterior sutures are placed to complete the anastomosis. These sutures are tied at the end to allow better visualization of the anastomosis. Finally, the 2-0 silk are used to complete the anterior outer layer by taking seromuscular bites of the jejunum.

59.3.6 Hepaticojejunostomy

An end-to-side hepaticojejunostomy is performed either in a continuous fashion for a large duct (>8 mm) or in an interrupted fashion for a small duct (<8 mm) and a stent is placed.

We sharply cut the bile duct staple line to ensure bleeding and we create an enterotomy in the jejunum slightly smaller than the bile duct, 10 cm distal to the pancreaticojejunostomy. For continuous anastomosis, we use two 4-0 V-loc sutures from the right lateral edge to medially. First the posterior raw is performed and then the anterior one until both overlap. Finally, both sutures are tied together.

For interrupted anastomosis, we use 5-0 polydioxanone or 5-0 polyglyconate sutures (Fig. 59.3b). After placing a right corner stitch and retracting it to expose the anastomosis, we start placing sutures posteriorly and tying them down. Then the anterior raw of sutures is placed laterally to medially without tying them initially to maintain good visualization of the anastomosis. At the end, the sutures are tied down and the anastomosis is completed.

59.3.7 Gastrojejunostomy

The jejunum is marked 40 cm distal to the hepaticojejunostomy with 2 sutures to be able to identify the correct orientation. Then the transverse colon is retracted cephalad to find the divided ligament of Treitz. The excess jejunum is reduced through the defect and it is brought up in an antecolic fashion to perform a 2-layer end-to-side hand-sewn isoperistaltic gastrojejunostomy (Fig. 59.3c). The stomach is grasped along the lesser curvature with P3 and moved medially and superiorly toward the left lateral sector of the liver, this maneuver creates appropriate tension and

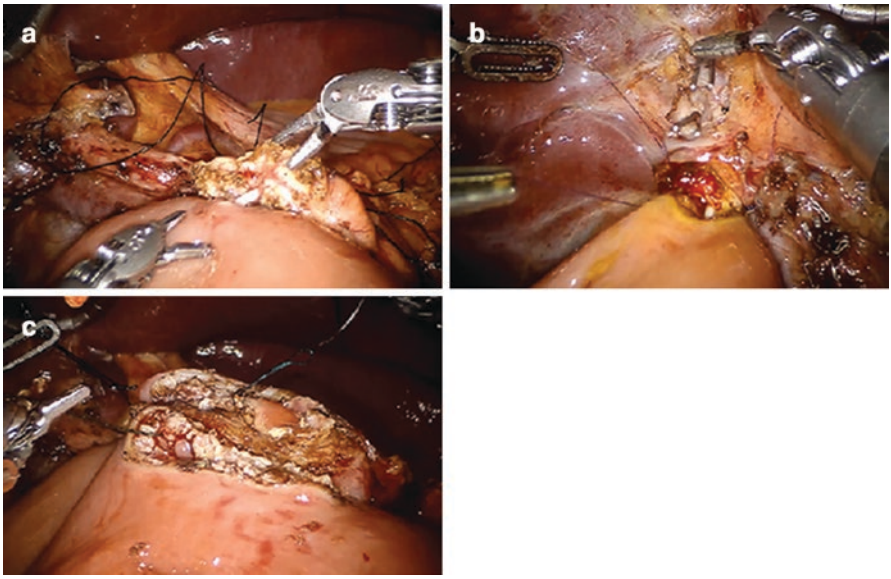

Fig. 59.3 (**a**) Pancreaticojejunostomy. (**b**) Hepaticojejunostomy. (**c**) Gastrojejunostomy

facilitates exposure. The posterior raw is created using 2-0 silk interrupted Lembert sutures. The robotic monopolar curved scissor is used to cut 4 cm of the gastric staple line and to create an enterotomy. Two 3-0 V-loc are used to create the inner layer. The posterior layer is performed in a continuous fashion while the anterior one is done using a running Connell stitch. Finally, the outer layer is completed with interrupted 2-0 silk Lembert sutures.

At the end of the procedure, a 19-French channeled drain is placed posterior to the hepaticojejunostomy and anterior to the pancreaticojejunostomy through the P3 trocar and the fascia of the extraction site and the 12 mm trocar are closed with #1 Polysorb sutures. Postoperatively, the patient management follows the enhanced recovery pathway.

59.4 Robotic Distal Pancreatectomy

Similar to robotic pancreaticoduodenectomy, the patient is positioned on a split-leg table with the legs abducted. The left arm tucked, and the right one is placed on an arm board. The operative table is placed in steep Trendelenburg and rotated 45 degrees away from the anesthesia to allow for the Da Vinci® SI robot to be docked at the head of the table. If the XI is used, the robot can be docked from the side of the patient.

The abdomen is accessed via an incision in the left upper quadrant along the midclavicular line using a 5 mm zero-degree scope and an optical separator trocar. After performing a diagnostic laparoscopy to rule out metastatic disease, 6 additional ports are placed. The robotic ports are placed in a mirror image to the

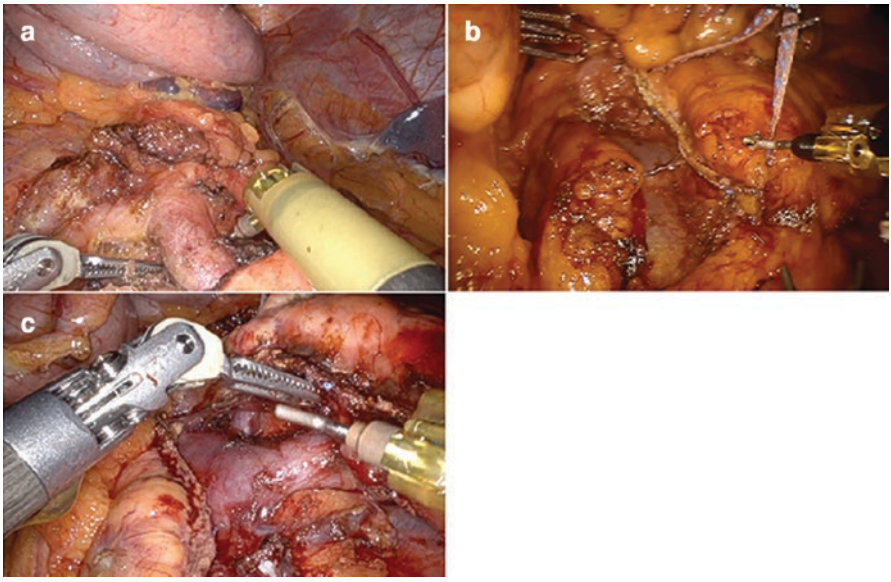

Fig. 59.4 (**a**) The dissected splenic artery. (**b**) After transection of the pancreas, the umbilical tape can be used as a handle to retract the gland. (**c**) Splenic vein dissected circumferentially

pancreaticoduodenectomy—as depicted in Fig. 59.1b—while the assistant ports are positioned in a similar fashion.

We perform the initial part of the operation laparoscopically. The lesser sac is opened by taking down the gastrocolic ligament with the Ligasure™ making sure to preserve the right gastroepiploic vessels. Then the short gastric vessels are divided to fully expose the pancreas. Next, we mobilize the left and transverse colon by taking down the white line of Told, the splenocolic and splenorenal ligaments. At this point, the liver retractor is placed under the stomach to allow for a good visualization of the celiac axis and the pancreas. The robot is docked. Next, the splenic artery is dissected circumferentially, and a vessel loop is used to encircle the artery (Fig. 59.4a). A bulldog is used to occlude the vessel and confirm that there is flow to the hepatic artery. Usually the left gastric vein is encountered during the splenic artery dissection and is divided with the Ligasure™. The splenic vein is dissected at the inferior border of the pancreas, encircled with a vessel loop and finally a tunnel is created behind the pancreas. An umbilical tape is placed around the pancreas, this will serve as a handle to facilitate pancreatic parenchymal engagement with the stapler which is fired using a 60 GIA purple load (Fig. 59.4b). Then, using a 45 GIA gold load with a curved tip, the artery is divided followed by the vein (Fig. 59.4c). While holding the staple line of the specimen and retracting it anteriorly, the attachments of the pancreas to the retroperitoneum are divided using the Hook cautery. Finally, the spleen is mobilized by dividing its suspending ligaments and the pancreas-spleen unit is extracted through the left lower quadrant 12-mm port incision.

At the end of the procedure, a 19-French channeled drain is placed through the P1 trocar and the fascia of the extraction site and the 12 mm trocar are closed with

#1 Polysorb sutures. Postoperatively, the patient management follows the enhanced recovery pathway.

59.5 Robotic Distal Pancreatectomy with En Bloc Resection of the Celiac Trunk (DP-CAR)

Patient position and port placement are similar to robotic distal pancreatectomy (Fig. 59.1b). Similarly, the lesser sac is entered, and the left/transverse colon is mobilized. The stomach is then retracted to expose the neck and the body of the pancreas. The common hepatic artery (CHA) is followed along the superior border of the pancreas to identify the GDA. Then the CHA is clamped and blood flow in the proper, right and left hepatic arteries is confirmed using the robotic ultrasound. If there is a triphasic flow in these vessels, the operation can proceed in a robotic fashion. If not, then we convert to an open procedure as this scenario will require a jump graft from the aorta to the proper hepatic artery.

The splenic artery is identified and transected at the tail as the proximal part is usually encased by the tumor, then the splenic vein is divided followed by the pancreatic parenchyma to the left of the GDA.

The CHA artery is transected while preserving the GDA origin (Fig. 59.5a). Then it is followed proximally to the left gastric vessels which are transected then to the celiac axis. At this point the aorta is exposed superior to the celiac trunk and inferiorly until the SMA is exposed posterior to the pancreas. The location of the SMA and celiac axis are confirmed with the robotic ultrasound. After clearing all lymphatics and perineural tissues surrounding the aorta and celiac axis, the origin of the celiac axis is transected using a stapler (GIA 45 mm gold vascualr load) (Fig. 59.5b). Finally, the specimen is extracted through the left lower quadrant 12-mm port incision.

At the end of the procedure, a 19-French channeled drain is placed through the P1 trocar and the fascia of the extraction site and the 12 mm trocar are closed with #1 Polysorb sutures. Postoperatively, the patient management follows the enhanced recovery pathway.

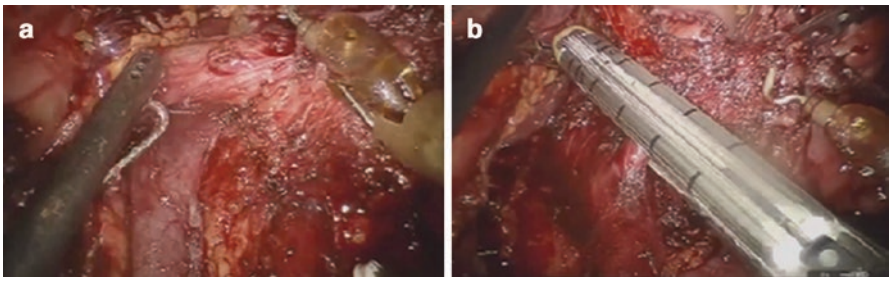

Fig. 59.5 (**a**) Common hepatic artery exposed and ready to be transected with care taken to protect the GDA. (**b**) Transection of the celiac artery at its base

59.6 Miscellaneous Robotic Pancreatic Surgery

The robot can be used for any pancreatic operation as long as the surgeon has an adequate expertise in pancreatic procedures and in using the robotic platform. We have previously described how to use the robot to perform:

1. Cyst-gastrostomy with debridement of infected necrotic pancreatic tissue and continued drainage into the stomach.
2. Total pancreatectomy with or without auto islet transplantation for chronic pancreatitis.
3. Puestow, Frey and Beger procedures for chronic pancreatitis.

59.7 Conclusion

In conclusion, the robotic platform can be safely and effectively used to perform a wide variety of pancreatic procedures in the hands of experienced and high-volume surgeons. Training in expert centers with a formalized curriculum is important to start a successful robotic pancreatic program and can potentially help to decrease the challenges encountered during the early adaption phase.

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References

1. Kowalsky SJ, Zenati MS, Steve J, et al. A combination of robotic approach and ERAS pathway optimizes outcomes and cost for pancreatoduodenectomy. Ann Surg. 2019;269(6):1138–45.
2. Magge DR, Zenati MS, Hamad A, et al. Comprehensive comparative analysis of cost-effectiveness and perioperative outcomes between open, laparoscopic, and robotic distal pancreatectomy. HPB. 2018;20:1172–80.
3. McMillan MT, Zureikat AH, Hogg ME, et al. A propensity score-matched analysis of robotic vs. open pancreatoduodenectomy on incidence of pancreatic fistula. JAMA Surg. 2017;152:327–35.
4. Zureikat AH, Borrebach J, Pitt HA, et al. Minimally invasive hepatopancreatobiliary surgery in North America: an ACS-NSQIP analysis of predictors of conversion for laparoscopic and robotic pancreatectomy and hepatectomy. HPB. 2017;19:1–8.
5. Girgis MD, Zenati MS, Steve J, et al. Robotic approach mitigates perioperative morbidity in obese patients following pancreaticoduodenectomy. HPB. 2017;19:1–6.
6. Zureikat AH, Postlewait LM, Liu Y, et al. A multi-institutional comparison of perioperative outcomes of robotic and open pancreaticoduodenectomy. Ann Surg. 2016;264:640–9.
7. Boone BA, Zenati M, Hogg ME, et al. Assessment of quality outcomes for robotic pancreaticoduodenectomy: identification of the learning curve. JAMA Surg. 2015;150:416–22.
8. Shakir M, Boone BA, Polanco PM, et al. The learning curve for robotic distal pancreatectomy: an analysis of outcomes of the first 100 consecutive cases at a high-volume pancreatic centre. HPB. 2015;17:580–6.
9. Zureikat AH, Moser JA, Boone BA, et al. 250 robotic pancreatic resections. Ann Surg. 2013;258:1–19.
10. Daouadi M, Zureikat AH, Zenati MS, et al. Robot-assisted minimally invasive distal pancreatectomy is superior to the laparoscopic technique. Ann Surg. 2013;257:128–32.
11. Nassour I, Choti MA, Porembka MR, et al. Robotic-assisted versus laparoscopic pancreaticoduodenectomy: oncological outcomes. Surg Endosc. 2018;32:2907–13.
12. Nassour I, Wang SC, Porembka MR, et al. Conversion of minimally invasive distal pancreatectomy: predictors and outcomes. Ann Surg Oncol. 2017;24:3725–31.
13. Nassour I, Wang SC, Christie A, et al. Minimally invasive versus open pancreaticoduodenectomy: a propensity-matched study from a National Cohort of patients. Ann Surg. 2017;268:1.
14. Nassour I, Wang SC, Porembka MR, et al. Robotic versus laparoscopic pancreaticoduodenectomy: a NSQIP analysis. J Gastrointest Surg. 2017;21:1784–92.
15. Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami International evidence-based guidelines on minimally invasive pancreas resection. Ann Surg. 2020;271:1–14.
16. Lee S, Allen PJ, Sadot E, et al. Distal pancreatectomy: a single institution's experience in open, laparoscopic, and robotic approaches. J Am Coll Surg. 2015;220:18–27.
17. Raoof M, Nota CL, Melstrom LG, et al. Oncologic outcomes after robot-assisted versus laparoscopic distal pancreatectomy: analysis of the National Cancer Database. J Surg Oncol. 2018;118:651–6.

Chapter 60
The Role of Surgery in Oligo-Metastatic Pancreatic Cancer

Florian Gebauer, Alexander Ioannis Damanakis, Felix Popp, and Christiane Bruns

Take Home Messages
- Role of surgery in oligometastastic pancreatic cancer remains unclear
- No prospective trials are currently available
- Retrospective data show a potential survival advantage in highly selected patients

Pearls and Pitfalls
- Definition of oligometastatic disease in pancreatic cancer still unclear
- Role of surgery in intraoperatively detected single metastasis not clear
- Type and duration of perioperative chemotherapy are not defined
- Routine surgery cannot be recommended based on the available data

Future Perspectives
- Proper definition of oligometastatic disease is needed
- Prospective trials are needed to define role of surgery in the oligometastatic setting

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60.1 Introduction

According to the guidelines of the National Comprehensive Cancer Network (NCCN), local therapy procedures are not recommended in the presence of distant metastases [1, 2]. The guidelines do not distinguish between the location, number, synchronous or metachronous metastases and recommend palliative chemotherapy for all patients with pancreatic cancer in stage IV. For this reason, synchronous or metachronous metastatic resections in pancreatic carcinoma are only performed in rare exceptional cases and do not correspond to current practice in contrast to other metastatic cancers, such as liver or lung metastasis from colorectal cancer.

The concept of oligometastasis (Box 60.1) has so far not been applied in staging and treatment decisions for pancreatic carcinoma. Recently, an attempt has been made to define subgroups of patients within the M1 group that are to be considered oligometastasized. It was found that patients with a maximum of 4 metastases in a single organ, together with CA 19–9 baseline <1000 U/mL and response or stable disease after first-line chemotherapy are most likely to be defined as oligometastatic patients [6].

Box 60.1 Oligometastasis
It defines an intermediate stage between limited and metastatic disease, being characterized by the presence of fewer than 5 metastases [3, 4]. However, synchronous oligometastases (sync-OM) and metachronous oligometastases (oligo-recurrence) have a different oncologic significance: the primary site is already controlled in the presence of an oligorecurrence but sync-OM might be the 'tip of the iceberg' [5]. In oligo-recurrence, the time between primary treatment and recurrence might give an idea of the tumor biology whereas in sync-OM disease there is no information about the distinct aggressiveness of the malignancy.

Nevertheless, operations in this patient-group, in contrast to the recommendations of the guidelines, are carried out in individual cases and the results are published in smaller case series [7–10]. In the following, the current state of research and evidence level for patients in the oligometastasized stage of pancreatic carcinoma will be presented.

60.2 Para-Aortic Lymph Node Metastases

Para-aortic lymph node metastases are generally regarded as extra-regional metastases and thus as distant metastases (M1) [11]. The prognostic value of this lymph node group is still controversially discussed. A meta-analysis of 13 studies found a reduced overall survival in the group with positive para-aortic lymph nodes compared to those without [12]. The median survival ranged between 15 and 36 months in the group without para-aortic lymph node metastasis and 6–17 months in the group with evidence of M1 lymph node metastasis. This results in a hazard ratio according to the

meta-analysis of 1.84 for tumor-related death with detection of interaorto-caval lymph node metastases. These data could be confirmed in a previous analysis [13].

Presence of M1 lymph node stations is thus undisputedly associated with a significantly worse prognosis in patients, but the question of whether resection would provide a survival advantage cannot be answered. So far, there is no study comparing the course of disease in patients who underwent resection with positive evidence of para-aortic lymph nodes to patients where lymph nodes were left in situ. Therefore, all available studies in which this particular lymph node region was surgically removed, resection can only be considered as an extended pathological staging [14]. The question of whether a primary tumor resection should be performed if this lymph node station is found to be positive cannot be answered conclusively either. A recent study by the Heidelberg research group showed a median overall survival of 12.3 months after tumor resection and resection of positive para aortic lymph nodes [10]. Compared to detection of distant metastases in parenchymal organs (liver, lungs) the prognosis of M1 lymph nodes seems to be better but worse than in the N+ stage of locoregional lymph nodes.

60.3 Hepatic Metastases

The liver is the most frequent site of metastasis of pancreatic carcinoma, both in the meta- and synchronous situation [15]. The tumor cells first reach the liver via the portal venous drainage system before reaching other organ systems via the caval vein. Therefore, metastasis pattern in this case is similar to that of other gastrointestinal tumors. Due to better imaging modalities (CT, MRI, contrast enhanced ultrasound), the number of hepatic metastases detected preoperatively has increased, avoiding futile surgery in patients with disseminated disease. However, in a proportion of patients the hepatic metastases are only visible intraoperatively, with no visible metastases despite use of multimodal imaging. In about 12% of patients, hepatic metastases are not detected preoperatively, primarily due to small lesions (<5 mm) or in patients with morphological situations that make diagnosis difficult (e.g. intrahepatic cholestasis, multiple liver cysts, benign liver tumors) [12].

The therapy of this group of patients regularly exhibit a particular challenge to the clinician, especially if the findings are few and technically easy to resect in combination with a well resectable primary tumor.

60.3.1 Liver Surgery for Metastasis

The evidence level for resections of synchronous or metachronous metastatic lesions in pancreatic cancer is weak. An overview of the current available studies is given in Table 60.1. The first study included 11 patients with resection of hepatic metastases in whom a significant survival advantage was found compared to patients who only underwent exploratory laparotomy [7]. In the group of patients with metastatic

Table 60.1 Overview of the studies with the largest patient cohorts with primary tumor and metastatic resection

Author [ref]	year	number (N)	Type of resection	Median OS	Mortality	Morbidity
Klempnauer	1996	20	S oder M	8.3	n.a.	n.a.
Gleisner [18]	2007	17	S	5.9	9.1%	45.5%
Shrikande [7]	2007	11	S	11.4	0.0%	24.5%
De Jong [16]	2010	20	S oder M	13.0	n.a.	1.0%
Klein [17]	2012	22	S	7.6	0.0%	18.0%
Tachezy [9]	2016	69	S	13.4	1.0%	68%
Hackert [10]	2017	128 (85)[a]	S oder M	12.3[a]	2.9%	45%

Resection type S synchronous metastasis resection, *M* metachronous resection, *Median OS* median overall survival, *n/a* not specified

[a]The study included 85 patients with hepatic metastasis, data refer exclusively to this patient collective

resection a median overall survival of 11.4 months was found compared to 5.9 months in the control group. The other studies included were smaller series and case reports, however, overall Shrikande's data could be confirmed in meta-analysis [8]. Another retrospective study revealed in 20 patients a median survival of 13.0 months after resection of metastases and primary tumors [16]. The extent of metastasis resection included the entire spectrum of liver resection procedures, in the majority atypical resections were performed (n = 22), with fewer anatomical segment resections (n = 6) and major hepatectomies (n = 4). Another study with 22 patients was able to find a median overall survival of 7.6 months without a control group [17]. An international multi-center study conducted by the Hamburg working group in 2016 identified 69 patients with resection of synchronous metastatic lesions who were compared to a control group of patients with palliative bypass surgery [9]. A median survival of 13.6 months was found in the resection group, which was significantly longer than 7.0 months in the palliative bypass group. The median number of resected metastases was 2 (range 2–11 metastases). The largest series on this topic to date has been published by the Heidelberg research group. Here 128 patients in the M1 stage underwent resection of the primary tumor and distant metastases [10]. The collective was divided into 85 patients with hepatic metastases and 43 patients with para-aortic lymph node metastases. Survival data of a control group are not provided, but median overall survival was identical for both metastatic groups at 12.3 months. In the majority of cases resection of synchronous hepatic metastases was performed (73%), for the group of metachronous resections the period between primary surgery and metastasis resection was not given.

60.3.2 Metachronous Liver Metastasis

Whether patients benefit from a metachronous metastasis resection cannot be answered on the basis of the available study data. Another study showed a shortened overall survival in the case of a metachronous resection compared to a simultaneous resection procedure (8.3 vs. 5.8 months) [19]. Whether the data can be transferred

to today's surgical and multimodal therapy concepts must, however, be viewed critically.

In the majority of the studies mentioned, both perioperative morbidity and mortality rates are reported [8–10, 16, 17]. What all studies have in common is that both morbidity and mortality are within an acceptable range for pancreatic surgery and do not differ significantly from those of pancreatic resections alone. Postoperative complications typical for pancreatic surgery, such as pancreatic fistulas, postoperative bleeding and delayed gastric emptying, were leading. Postoperative complications specific liver surgery such as biliomas were rare and did not occur to a clinically significant extent.

60.3.3 Ablation Techniques

In the therapy of hepatic metastases, the use of local ablative methods has proven successful and is of particular importance for colorectal liver metastases but also for liver tumors in the case of functional irresectability. Microwave ablation (MWA) and radiofrequency ablation (RFA) are primarily used here. In contrast to the treatment of colorectal cancer, the level of evidence for metastatic ablation in pancreatic cancer is low [20]. There was no primary tumor resection. A modern therapy concept was recently published from the Mayo Clinic in Jacksonville. Patients in the hepatic oligometastasized stage were first treated with induction chemotherapy using the FOLFIRINOX regimen or gemcitabine + nab paclitaxel. Subsequently, primary tumor resection was performed and in 4/6 patients RFA of liver metastases, the remaining 2 patients were resected. A median survival of 2.7 years was observed which was identical in this study to the median survival of patients without distant metastases [21].

60.4 Pulmonary Metastases

Patients with a single organ pulmonary metastasis appear to differ in their oncological course from patients with liver metastases. This group of patients is rare, only about 3% of the patients show exclusively pulmonary metastases in the course of the disease after resection of the primary tumor [22]. However, the tumor biology of this group of patients seems to vary from that of other metastatic sites. A recent study from the Johns Hopkins University shows a median overall survival of 23 months after diagnosis of pulmonary metastases, which increases to 51 months after metastasectomy ($p = 0.04$) [22]. A study by Krueger and colleagues investigated the course of pulmonary metastases after primary tumor resection. The 40 patients examined showed a median survival of 25.5 months after diagnosis of metastases, which appears to be dependent on the number of metastases: patients with less than 10 metastases and unilateral occurrence had significantly better survival than patients with >10 metastases or bilateral involvement (31.3 vs. 18.7 and 31.3 vs. 21.8 months, $p < 0.05$) [23]. A study from Japan collected case reports from

the years 1983–2004 and analyzed them in a meta-analysis. The median overall survival after metastasis resection was 37 months, the 3 and 5 year survival was 50% and 41%, respectively. Again, patients with pulmonary metastases <16 mm who underwent lobectomy had a significantly longer overall survival compared to the control group (83 vs. 16 months, p = 0.04) [24].

60.5 Current Data and Recommendations

According to currently valid guidelines, local resection procedures are not recommended in the metastatic stage of pancreatic carcinoma [1, 2]. At the time of diagnosis, the majority of patients show a polytopic metastasis pattern with many metastases and often more than one organ system affected. Surgical procedures are not feasible for these patients, as tumor clearance cannot be achieved in this patient group. Even if this would be the feasible in exceptional cases, the question of the oncological benefit arises.

For the significantly smaller group of patients in the oligometastatic tumor stage, however, it is worth taking a differentiated look at the currently available evidence. Even though the overall evidence level is low, there is increasing data that there may be subgroups within stage IV patients that might benefit from primary tumor and metastasis resection, especially in the setting of modern multimodal therapy regimens.

With the introduction of highly effective chemotherapy regimens such as the FOLFIRINOX, gemcitabin/nab-paclitaxel combination or liposomal irinotecan (nal-IRI), survival in the palliative situation was significantly prolonged compared to gemcitabine standard therapy [25–27]. With overall survival between 9 and 13 months, the survival rates are approximately in the range that the previously listed studies following resection of metastases could also show. Common to all studies is a high selection bias, the indication for surgery or palliative chemotherapy is retrospectively not evaluable in all cases, in addition, various chemotherapy regimes were used so that a direct comparison of survival data is not feasible. However, it is obvious that in the majority of the studies an overall survival between 12 and 14 months could be shown for the patients in an oligmetastasized stage which differed only insignificantly between the studies.

A resection of metastases can still not be recommended on the basis of the available data. However, the dogma of categorical rejection of surgical treatment options in the metastatic stage should be questioned in some cases. If such a procedure is decided upon within the framework of an interdisciplinary consensus, the patients should be embedded in a multimodal therapy concept, in the sense of a preoperative induction chemotherapy and in the case of a stable tumor finding a secondary resection should be aimed at. However, no data are currently available for this concept, so that the oncological benefit cannot be assessed beyond the individual experience of a few individual cases.

60.6 Conclusions

The available data clearly show the need for prospective studies to assess the role of surgery in multimodal therapies in the metastatic stage. Based on the currently available data, a general recommendation cannot be made for metastatic resection neither in the syn- nor metachronous stage and will, outside studies, continue to be reserved for highly selected patients in the sense of an individual therapy concept.

References

1. Seufferlein T, et al. S3-guideline exocrine pancreatic cancer. Z Gastroenterol. 2013;51(12):1395–440.
2. Tempero MA, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2014;12(8):1083–93.
3. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378–82.
4. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.
5. Yamashita H, et al. Lung stereotactic radiotherapy for oligometastases: comparison of oligo-recurrence and sync-oligometastases. Jpn J Clin Oncol. 2016;46(7):687–91.
6. Damanakis AI, et al. Proposal for a definition of "Oligometastatic disease in pancreatic cancer". BMC Cancer. 2019;19(1):1261.
7. Shrikhande SV, et al. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2007;14(1):118–27.
8. Michalski CW, et al. Resection of primary pancreatic cancer and liver metastasis: a systematic review. Dig Surg. 2008;25(6):473–80.
9. Tachezy M, et al. Synchronous resections of hepatic oligometastatic pancreatic cancer: disputing a principle in a time of safe pancreatic operations in a retrospective multicenter analysis. Surgery. 2016;160(1):136–44.
10. Hackert T, et al. Radical surgery of oligometastatic pancreatic cancer. Eur J Surg Oncol. 2017;43(2):358–63.
11. van Roessel S, et al. International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg. 2018;153:e183617.
12. Paiella S, et al. The prognostic impact of para-aortic lymph node metastasis in pancreatic cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2016;42(5):616–24.
13. Komo T, et al. Prognostic impact of para-aortic lymph node micrometastasis in pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2016;23(6):2019–27.
14. Sho M, et al. Postoperative prognosis of pancreatic cancer with Para-aortic lymph node metastasis: a multicenter study on 822 patients. J Gastroenterol. 2015;50(6):694–702.
15. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med. 2008;132(6):931–9.
16. de Jong MC, et al. Safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. J Surg Oncol. 2010;102(3):256–63.
17. Klein F, et al. The impact of simultaneous liver resection for occult liver metastases of pancreatic adenocarcinoma. Gastroenterol Res Pract. 2012;2012:939350.
18. Gleisner AL, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? Cancer. 2007;110(11):2484–92.
19. Klempnauer J, et al. Is liver resection in metastases of exocrine pancreatic carcinoma justified? Chirurg. 1996;67(4):366–70.

20. Hua YQ, et al. Radiofrequency ablation for hepatic oligometastatic pancreatic cancer: an analysis of safety and efficacy. Pancreatology. 2017;17(6):967–73.
21. Kandel P, et al. Survival of patients with oligometastatic pancreatic ductal adenocarcinoma treated with combined modality treatment including surgical resection: a pilot study. J Pancreat Cancer. 2018;4(1):88–94.
22. Arnaoutakis GJ, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. J Gastrointest Surg. 2011;15(9):1611–7.
23. Krüger et al. Isolated pulmonary metastases define a favorable subgroup in metastatic pancreatic cancer. Pancreatology. 2016;16(4):593–8. https://doi.org/10.1016/j.pan.2016.03.016. Epub 2016 Mar 30.
24. Nakajima M, et al. Novel indications for surgical resection of metachronous lung metastases from pancreatic Cancer after curative resection. J Clin Gastroenterol. 2017;51(5):e34–8.
25. Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
26. Wang-Gillam A, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545–57.
27. Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.

Chapter 61
Total Pancreatectomy

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Take Home Messages

- Case selection for total pancreatectomy is challenging, regardless of the type of disease or indication.
- Total pancreatectomy should be avoided if another organ-preserving surgical procedure is applicable.
- Postoperative care after total pancreatectomy is demanding.
- Patient education and compliance are paramount, in particular to prevent potentially fatal hypoglycemia.

Pearls and Pitfalls

Pearls:

- Avoidance of pancreatic anastomosis and associated risks of morbidity and mortality
- Curative approach in case of diseases affecting the whole organ

Pitfalls:

- Lifelong complications of exocrine and endocrine insufficiency, especially hard to control, brittle diabetes mellitus

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Future Perspectives

- Better definition of the extent of resection for main-duct intraductal-papillary mucinous neoplasia (IPMN); better localization of areas with high risk of malignant progression.
- Further genetic research to identify individuals with high risk for pancreatic cancer (e.g. familial pancreatic cancer) that might benefit from prophylactic pancreatectomy.
- Maintaining better long-term graft function in cases of total pancreatectomy and islet cell auto-transplantation.

61.1 Introduction

Depending on the underlying pathology (e.g. benign or malignant) and its location within the gland, there is a wide range of operative techniques for the surgical treatment of pancreatic diseases. Total pancreatectomy (TP) is one of them, which entails the complete removal of the organ. While there is no need for a potentially complex pancreatic anastomosis, the procedure carries the significant drawback of lifelong metabolic insufficiencies of the endocrine and the exocrine function of the pancreas.

The first reported TP cases are from Rockey in a patient with carcinoma in 1943 [1] and from Priestley in a patient with hyperinsulinism in 1944 [2], showing the feasibility of this resectional approach. Following these reports, three of Whipple's original five cases of chronic pancreatitis reported in 1946 were treated with a total pancreatectomy [3]. TP was introduced again in 1954 by Ross [4] and then by Porter in 1958 [5] and its popularity increased in the 1960s. In 1960, Howard and Jordan reported the first series of patients that underwent TP [6]. The perioperative mortality rate was 37%, which indicated that TP was a high-risk operation with morbidity and mortality rates similar to a Whipple's resection at that time. In addition to avoiding a pancreatic anastomosis, TP was for some time also considered an extension of oncological radicality in patients with pancreatic cancer in larger series from the late 1980s and 1990s [7–12]. However, TP for malignancy did not improve survival rates compared to other pancreatic resections and had no benefits regarding perioperative mortality rates. In contrast, TP led to a worse quality of life, as a result of exocrine and endocrine deficiency [13]. Besides unstable and difficult to control blood glucose levels, other impacting metabolic problems were severe diarrhea leading to weight loss through malabsorption and cachexia with vitamin D insufficiency leading to osteopathy.

Recently, there has been an increase in total pancreatectomy rates for different indications because of markedly decreased surgical complication rates and better options to manage endo- and exocrine insufficiency, in particular pancreatic enzyme preparations and long-acting insulin products [14–17].

61.2 Indications

TP is mainly indicated for main duct intraductal papillary mucinous neoplasms (IPMN) or for pancreatic cancer located close to or at the neck of the pancreas. There are also rarer indications such as chronic pancreatitis and—in particular—hereditary pancreatitis, or multifocal tumors, such as neuroendocrine tumors of the pancreas or renal cell carcinoma metastasis.

Rather than planned before the operation as in the mentioned scenarios, the indication to perform a TP is often made intraoperatively, e.g. to prevent pancreatic fistula as a result of a high-risk pancreatic anastomosis in cases of a soft and/or fatty pancreatic parenchyma and a non-dilated pancreatic duct, or because of positive resection margins on frozen sections.

TP is a major procedure with potentially severe complications, but for selected cases perioperative mortality is low and long-term overall morbidity is acceptable [14–26]—see Sect. 61.4.

61.2.1 Intraductal Papillary Mucinous Neoplasm

The prevalence of cystic pancreatic lesions is estimated between 2% and 45% of the normal population in radiological series [27–31]. Up to 70% of these are intrapapillary mucinous neoplasms (IPMN) [32]. IPMN are classified into three sub-types, which are the main duct IPMN (MD-IPMN), the branch duct IPMN (BD-IPMN) and the mixed type IPMN. According to large series, invasive carcinoma is seen in 11–30% of cases with BD-IPMNs and in 33–60% of cases with MD-IPMNs [33–37].

According to the current guidelines of the European Study Group on Cystic Tumours of the Pancreas [38], surgery should be considered in all cases of MD-IPMN and mixed-type IPMN, because of the high rate of malignancy. Resection is advised for MD-IPMN with a duct diameter larger than 5 mm, and total pancreatectomy can be considered in this setting, if there are mural nodules within the main pancreatic duct, or in high risk patients, for example with a positive family history of pancreatic cancer. In contrast, the international Fukuoka consensus guidelines recommend surgical resection for MD-IPMN with a duct diameter larger than 10 mm or in cases with mural nodules, positive cytology, and for patients that present with jaundice [39]. A duct diameter between 5 and 9 mm is considered a 'worrisome feature' with recommendations to close follow-up, but not immediate resection.

The indications for total pancreatectomy are based on the degree of main pancreatic duct dilatation, mural nodules, and presence of symptoms. Clearly the goal of surgery is to achieve complete removal of the tumor, but patients must also be able to deal with the resulting 'brittle' diabetes mellitus and exocrine insufficiency. In fit

patients, indications for total pancreatectomy are outlined above, and TP should also be considered at the time of the operation if frozen sections of the resection margin are positive for (high-grade) dysplasia. It remains a matter of debate whether TP is also indicated in case of low-grade dysplasia or without dysplasia but IPMN at the margin, or whether in those cases close surveillance is sufficient. Further, in cases of invasive pancreatic cancer arising from IPMN, TP is often not advised as the prognosis is determined by pancreatic cancer and not the remaining IPMN in most instances.

In general, complete removal of the pancreas can be avoided in MD-IPMN, especially when the risks of the procedure outweigh its advantages.

61.2.2 Pancreatic Cancer

Locally advanced pancreatic cancer is the most common indication for performing a TP [19, 24–26, 40]. Despite metabolic drawbacks after surgery, current studies show that overall median survival is similar to that of partial pancreaticoduodenectomy and as high as 21 months [24]. In a recent study, Hartwig et al. reported about the indications for TP in 377 patients with malignant pancreatic disease, which included 289 patients (76.7%) with pancreatic cancer. An intraoperative decision for TP was made in 115 patients (30.5%) because of tumor extension, in 138 patients (36.6%) because of margin positivity, in 38 patients (10.1%) because of the need for an arterial resection (and the increased risk with a combined pancreatic anastomosis), and in 46 patients (12.2%) because of the pancreatic texture (e.g. the pancreas was atrophic, soft or lipomatous), which can also lead to anastomotic problems postoperatively. Only 40 cases (10.6%) were preoperatively planned for a TP. According to this study, poor tumor grading, high AJCC tumor stage, age more than 70 years, an R1 resection, and simultaneous vascular resections were prognostic parameters for adverse long-term outcomes [22].

Satoi et al. reported in their series that in the TP group, there was higher-stage disease, a higher frequency of lymph node metastasis, and a lower adjuvant chemotherapy completion rate compared with the partial pancreaticoduodenectomy group, yet no differences in mortality and morbidity were observed [40]. A review of the National Cancer Data Base of 2582 pancreatic cancer cases showed that age, tumor size and grade, lymph node positivity, margin positivity, and adjuvant therapy significantly impacted survival rates for patients after TP. Here, median overall survival was low at 15 months [17].

In conclusion, total pancreatectomy may be required in selected pancreatic cancer resection cases, particularly in patients with large/central tumors, with (repetitive) positive margins, with extended (e.g. arterial) resections and when reconstruction seems to be associated with a high risk of a significant postoperative pancreatic fistula. While in recent series, overall survival is comparable to that after partial pancreatectomy, there are also data that survival is inferior. Thus, a careful risk-benefit assessment must be made preoperatively or during surgery.

61.2.3 Familial Pancreatic Cancer

Familial pancreatic cancer is an uncommon tumor syndrome, commonly defined as having at least two first degree relatives with pancreatic cancer [41]. Several genetic syndromes (e.g. Peutz–Jeghers syndrome) are associated with an increased risk of developing pancreatic cancer as well as other malignancies and diseases. In addition, in a significant number of cases the genetic cause of familial pancreatic cancer is currently unknown.

Schneider et al. classified individuals at risk with at least two first-degree relatives with confirmed pancreatic cancer in their 10-year experience from the German national case collection (FaPaCa) [42]. Here, the authors document their screening approach and recommend a prophylactic limited surgical resection for potential precursor lesions [43, 44]. Total pancreatectomy is only performed when there is cancer on frozen section, or multifocal high grade pancreatic intraepithelial neoplasia (PanIN) or intrapapillary mucinous neoplasia (IPMN). Total pancreatectomy might further be indicated in high risk individuals on a case-by-case basis as prophylactic surgery [45].

61.2.4 Chronic Pancreatitis

Chronic pancreatitis is a multi-factorial chronic inflammatory disease leading to chronic abdominal pain and often multiple hospitalizations with acute painful (pancreatitis) attacks. Patients with this condition develop diabetes mellitus and maldigestion as a result of progressive exocrine and endocrine insufficiency and have a higher risk to develop pancreatic cancer [46, 47]. Chronic pancreatitis is frequently associated with high alcohol consumption [48, 49].

Surgery for chronic pancreatitis involves partial resections or specific drainage operations (for indications and types of surgery, see [50, 51]). In general, surgical treatment for chronic pancreatitis is meaningful for patients with a (severe) pain syndrome, with an inflammatory/calcified mass in the pancreas, and/or with a dilated main pancreatic duct, and/or with organ complications such as bile duct obstruction and others. In those cases, total pancreatectomy is generally not required. However, even after drainage or resectional procedures, the debilitating pain syndrome might remain, and a completion (total) pancreatectomy might be considered on an individual basis.

In rare instances, chronic pancreatitis is a hereditary disease. Several gene mutations and variants have been identified that correlate with the risk to develop chronic pancreatitis. Long standing chronic pancreatitis has an increased risk of malignant transformation to pancreatic cancer (for example about 40%–55% lifetime risk in patients with autosomal dominant hereditary pancreatitis with a confirmed mutation in the gene encoding cationic trypsinogen (protease serine 1, PRSS1) [52, 53]. Especially in these cases, total pancreatectomy with islet autotransplantation (TPIAT)

has been suggested, to provide pain relieve and to prevent brittle diabetes mellitus [54, 55]. The main indication for TPIAT is therefore hereditary chronic pancreatitis, while it is rather controversial for non-hereditary chronic pancreatitis. The current International Consensus Guidelines [56] suggest careful patient selection with the main indication being recurrent pancreatitis refractory to medical treatment that limits the quality of life at a young age. In this group of patients TPIAT is preferred over TP alone when feasible, although long-term graft failure remains a problem.

61.3 Procedure

The operative procedure of total pancreatectomy follows similar steps as those for partial pancreaticoduodenectomy and distal pancreatectomy.

Entering the abdomen can be achieved by a bilateral subcostal or midline incision. The pancreas is exposed through entering the lesser sac. The duodenum is mobilized with a Kocher maneuver. Creating a retropancreatic tunnel above the superior mesenteric vein/portal vein may be necessary for a planned partial pancreatoduodenectomy, but for a preoperatively planned TP the pancreas can be fully mobilized from the portal and superior mesenteric veins later in the procedure following the principles of the uncinate process first approach and distal pancreatectomy. The hepatoduodenal ligament and the common hepatic artery are dissected to complete an en-bloc lymphadenectomy (in case of cancer) and preparation of the gastroduodenal artery. After the dissection of Calot's triangle, en-bloc or separate retrograde cholecystectomy is performed. The common hepatic duct is divided above the cystic duct insertion. The gastroduodenal artery is test-clamped and hepatic artery blood flow confirmed before dividing and ligating the gastroduodenal artery. An individualized approach needs to be taken in case of insufficient flow (e.g. vascular surgeon's assessment, intraoperative interventional procedure, bypass procedure etc.). Without proper arterial blood flow to the liver, the procedure should be abandoned. The spleen can be preserved, if technically feasible and if the indication of TP is not malignancy. When indicated to remove it because of multifocal or extended disease, the spleen is fully mobilized with division of the short gastric vessels for en-bloc resection to achieve adequate lymphadenectomy. The splenic artery is dissected and ligated close to its origin from the coeliac axis and the splenic vein is dissected and ligated behind the pancreas close to its insertion into the portal vein. Preserving the left gastric artery is then necessary to supply gastric arterial blood flow, which remains the dominant and potentially only source for the stomach. To avoid gastric congestion in these cases, it is advisable to preserve the coronary vein. If this is not possible and if the stomach is congested at reconstruction, it may be required to resect up to two thirds of the stomach. In such cases, a Roux-en-Y reconstruction will be necessary. Proximally, the post-pyloric duodenum or if needed the stomach, and distally, the proximal jejunum are divided. The proximal jejunal mesentery is prepared allowing reflection of the duodenum and proximal jejunum underneath the root of the small bowel mesentery into the supracolic compartment. The pancreas and uncinate process are then dissected of the portal vein

and the superior mesenteric artery following the principles of the uncinate process first approach [57] and following reflection of the pancreatic tail to the right by dissecting it from the retroperitoneal structures. Reconstruction is generally performed using a continuous limb with a retrocolic hepatico-jejunostomy and an antecolic gastro-jejunostomy.

61.3.1 Minimally Invasive Total Pancreatectomy

Total pancreatectomy with or without splenectomy can be carried out laparoscopically or robotically in selected patients. In comparison to partial pancreatoduodenectomy and distal pancreatic resection, data on the laparoscopic and robotic approach for TP are sparse, and therefore, there is currently no solid evidence on the superiority of the minimal-invasive approach. Nonetheless, the laparoscopic and robotic approach for TP appears to be feasible and safe [58, 59].

61.4 Outcomes

61.4.1 Perioperative Outcomes

Due to improvements in surgical techniques and postoperative management, the initially high perioperative morbidity and mortality rates have decreased significantly in the last two decades [14–17, 21]. In a large series from two high volume centers, morbidity was 59.3% and the 30-day mortality rate was 2.1% [60]. In another series, overall morbidity and 30-day mortality rates were 31.9% and 5.4%, respectively [61].

Advanced age (>70 years), the presence of comorbid conditions, long duration of the operation (>420 min), high blood loss (>2000 mL), and/or arterial resections were reported as independent risk factors for mortality following TP [22, 62].

Morbidity after TP are mostly surgical complications including delayed gastric emptying, postoperative hemorrhage, anastomotic leakage, intraabdominal abscesses and wound infections [21, 22].

Not surprisingly, compared to elective TPs, completion pancreatectomies for complications have significantly higher mortality (39% to 47% vs. 4.8% to 12.5%) and morbidity rates (79% to 100% vs. 46% to 54%) [16, 21].

61.4.2 Long-Term Outcomes

Late complications and morbidities of TP include diabetes mellitus and malabsorption due to endocrine and exocrine insufficiency, respectively, but also hepatic steatosis and anastomotic ulcers [16, 18, 22, 23].

Besides life threatening but easily underestimated hyper- and hypoglycemia (brittle diabetes mellitus) through a complete lack of endogenous insulin and glucagon [14, 21], diabetes mellitus after total pancreatectomy is also associated with the typical late complications like retinopathy, nephropathy, neuropathy and cardiac diseases, which results in decreased quality of life.

Diarrhea and/or steatorrhea due to exocrine insufficiency contributes to the loss of fat-soluble vitamins, especially vitamin D, magnesium, and trace elements, leading to malnutrition-related complications such as osteopathy and osteoporosis, as well as to hepatic steatosis [63].

Another important drawback of TP is the risk of an anastomotic ulcer, which can result in serious complications. Barbier et al. observed anastomotic ulcers with or without pylorus preservation, indicating that this complication is not influenced by the mode of reconstruction. Therefore, the authors strongly recommend life-long PPI treatment for all TP patients, since no anastomotic ulcer was observed after routine PPI administration [21, 64–66].

Indications for total pancreatectomy:

- Oncological (e.g. IPMN, pancreatic cancer): to achieve clear margins (e.g. centrally located pancreatic cancers, main-duct IPMN affecting the whole gland with high-grade dysplasia).
- Prophylactic (e.g. IPMN, hereditary chronic pancreatitis, familial pancreatic cancer): to prevent cancer development in case of main-duct IPMN, or hereditary CP, or familial pancreatic cancer.
- Technical: in cases where the pancreatic anastomosis is deemed unsafe with a high risk of leakage, or with concomitant vascular resections.
- Rescue: as completion pancreatectomy following pancreatic leak, or recurrent disease (either benign, or malignant).

Technical tips:

- Aim for en-bloc resection of the pancreas and avoid cutting the pancreas at the pancreatic neck in case of malignant or premalignant lesions (e.g. IPMN).
- Start dissection from right side with mobilisation of the duodenum to the left side for a spleen-preserving total pancreatectomy.
- Apply dissection from right to left or left to the right side for a total pancreatectomy with splenectomy.
- Priority should be given to the left gastric vessels to avoid any perfusion insufficiencies or venous congestion of the stomach.
- Be ready for an extra vascular anastomosis if there is inadequate flow after test-clamping the gastroduodenal artery.

61.5 Conclusion

Total pancreatectomy is a major procedure, with significant short and long-term sequalae. Although complications from the pancreatic anastomosis are avoided, morbidity and mortality rates are not different from other major pancreatic

resections. In general, total pancreatectomy should not be the first line treatment, if any other organ-preserving procedure is applicable.

If indicated, both surgeons and patients should anticipate the metabolic challenges of exocrine and especially endocrine insufficiency with the ensuing brittle diabetes mellitus. Therefore, case selection is challenging, regardless of the type of indication.

References

1. Rockey EW. Total pancreatectomy for carcinoma: case report. Ann Surg. 1943;16:1751–6.
2. Priestley JT, Comfort MW, Radcliffe J. Total pancreatectomy for hyperinsulinism due to an islet-cell adenoma: survival and cure at sixteen months after operation presentation of metabolic studies. Ann Surg. 1944;119:211–21.
3. Whipple AO. Radical surgery for certain cases of pancreatic fibrosis associated with calcareous deposits. Ann Surg. 1946;124:991–1008.
4. Ross DE. Cancer of the pancreas; a plea for total pancreatectomy. Am J Surg. 1954;87:20–33.
5. Porter MR. Carcinoma of the pancreaticoduodenal area; operability and choice of procedure. Ann Surg. 1958;148:711–23.
6. Howard JM, Jordan GL. Surgical disease of the pancreas. Philadelphia, PA: JB Lippincott; 1960.
7. Sarr MG, Behrns KE, van Heerden JA. Total pancreatectomy. An objective analysis of its use in pancreatic cancer. Hepatogastroenterology. 1993;40:418–21.
8. Grace PA, Pitt HA, Tompkins RK, et al. Decreased morbidity and mortality after pancreatoduodenectomy. Am J Surg. 1986;151:141–9.
9. McAfee MK, van Heerden JA, Adson MA. Is proximal pancreatoduodenectomy with pyloric preservation superior to total pancreatectomy? Surgery. 1989;105:347–51.
10. Launois B, Franci J, Bardaxoglou E, et al. Total pancreatectomy for ductal adenocarcinoma of the pancreas with special reference to resection of the portal vein and multicentric cancer. World J Surg. 1993;17:122–6.
11. Baumel H, Huguier M, Manderscheid JC, et al. Results of resection for cancer of the exocrine pancreas: a study from the French Association of Surgery. Br J Surg. 1994;81:102–7.
12. Ihse I, Anderson H, Andren-Sandberg A. Total pancreatectomy for cancer of the pancreas: is it appropriate? World J Surg. 1996;20:288–94.
13. Dresler CM, Fortner JG, McDermott K, et al. Metabolic consequences of (regional) total pancreatectomy. Ann Surg. 1991;214:131–40.
14. Billings BJ, Christein JD, Harmsen WS, et al. Quality-oflife after total pancreatectomy: is it really that bad on long-term follow-up? J Gastrointest Surg. 2005;9:1059–67.
15. Casadei R, Monari F, Buscemi S, et al. Total pancreatectomy: indications, operative technique, and results: a single Centre experience and review of literature. Updates Surg. 2010; 62:41–6.
16. Müller MW, Friess H, Kleeff J, et al. Is there still a role for total pancreatectomy? Ann Surg. 2007;246:966–74.
17. Johnston WC, Hoen HM, Cassera MA, et al. Total pancreatectomy for pancreatic ducal adenocarcinoma: review of the National Cancer Data Base. HPB. 2016;18:21–8.
18. Crippa S, Tamburrino D, Partelli S, et al. Total pancreatectomy: indications, different timing, and perioperative and long-term outcomes. Surgery. 2011;149:79–86.
19. Almond M, Roberts KJ, Hodson J, et al. Changing indications for a total pancreatectomy: perspective over a quarter of a century. HPB. 2015;17:416–21.
20. Casadei R, Ricci C, Monari F, et al. Clinical outcomes of patients who underwent total pancreatectomy. Pancreas. 2010;39:546–7.
21. Barbier L, Jamal W, Dokmak S, et al. Impact of total pancreatectomy: short- and long-term assessment. HPB. 2013;15:882–92.

22. Hartwig W, Gluth A, Hinz U, et al. Total pancreatectomy for primary pancreatic neoplasms. Renaissance of an unpopular operation. Ann Surg. 2015;261:537–46.
23. Watanabe Y, Ohtsuka T, Matsunaga T, et al. Long-term outcomes after total pancreatectomy: special reference to survivors' living conditions and quality of life. World J Surg. 2015;39:1231–9.
24. Casadei R, Ricci C, Tarufelli G, et al. Is total pancreatectomy as feasible, safe, efficacious, and cost-effective as pancreaticoduodenectomy? A single center, prospective, observational study. J Gastrointest Surg. 2016;20(9):1595–607.
25. Yang D, Xiong J, Liu X, et al. Total pancreatectomy compared with pancreaticoduodenectomy: a systematic review and meta-analysis. Cancer Manag Res. 2019;11:3899–908.
26. Xiong J, Wei A, Ke N, et al. A case-matched comparison study of total pancreatectomy versus pancreaticoduodenectomy for patients with pancreatic ductal adenocarcinoma. Int J Surg. 2017;48:134–41.
27. Ip IK, Mortele KJ, Prevedello LM, et al. Focal cystic pancreatic lesions: assessing variation in radiologists management recommendations. Radiology. 2011;259:136–41.
28. Girometti R, Intini S, Brondani G, et al. Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: prevalence and relation with clinical and imaging features. Abdom Imaging. 2011;36:196–205.
29. Chang YR, Park JK, Jang JY, et al. Incidental pancreatic cystic neoplasms in an asymptomatic healthy population of 21,745 individuals: large-scale, single-center cohort study. Medicine (Baltimore). 2016;95:e5535.
30. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183–97.
31. Salvia R, Fernández-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg. 2004;239(5):678–85.
32. Werner J, Fritz S, Buchler MW. Intraductal papillary mucinous neoplasms of the pancreas: a surgical disease. Nat Rev Gastroenterol Hepatol. 2012;9:253–9.
33. Crippa S, Fernandez-Del Castillo C, Salvia R, et al. Mucin-producing neoplasms ofthe pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clin Gastroenterol Hepatol. 2010;8:213–9.
34. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. Ann Surg. 2007;246:644–51, [discussion 51–4].
35. Fritz S, Klauss M, Bergmann F, Strobel O, Schneider L, Werner J, et al. Pancreatic main-duct involvement in branch-duct IPMNs. Ann Surg. 2014;260:848e56.
36. Nguyen AH, Toste PA, Farrell JJ, Clerkin BM, Williams J, Muthusamy VR, et al. Current recommendations for surveillance and surgery of intraductal papillary mucinous neoplasms may overlook some patients with cancer. J Gastrointest Surg. 2015;19:258e65.
37. Marchegiani G, Mino-Kenudson M, Sahora K, Morales-Oyarvide V, Thayer S, Ferrone C, et al. IPMN involving the main pancreatic duct: biology, epidemiology, and long-term outcomes following resection. Ann Surg. 2015;261:976–83.
38. The European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018;67:789–804.
39. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 2017;17:738–53.
40. Satoi S, Murakami Y, Motoi F, et al. Reappraisal of total pancreatectomy in 45 patients with pancreatic ductal adenocarcinoma in the modern era using matched-pairs analysis. Multicenter study group of pancreatobiliary surgery in Japan. Pancreas. 2016;45(7):1003–9.
41. Petersen GM. Familial pancreatic Cancer. Semin Oncol. 2016 October;43(5):548–53.
42. Schneider R, Slater EP, Sina M, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. Fam Cancer. 2011;10(2):323–30.
43. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol. 2006;4:766–81.

44. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol. 2009;104:2175–81.
45. Davis B, Lowy AM. Surgical management of hereditary pancreatic cancer. Med Clin North Am. 2000;84(3):749–59.
46. Wilson GC, Sutton JM, Smith MT, et al. Completion pancreatectomy and islet cell autotransplantation as salvage therapy for patients failing previous operative interventions for chronic pancreatitis. Surgery. 2015;158:872–80.
47. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010;24:349–58.
48. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120:682–707.
49. Braganza JM, Lee SH, McCloy RF, et al. Chronic pancreatitis. Lancet. 2011;377:1184–97.
50. Kempeneers MA, Issa Y, Ali UA, et al. International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis. Pancreatology. 2020;20(2):149–57. pii: S1424–3903(19)30802–6.
51. Kleeff J, Whitcomb DC, Shimosegawa T, et al. Chronic pancreatitis. Nat Rev Dis Primers. 2017;3:17060.
52. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology. 2013;144:1292–302.
53. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004;2:252–61.
54. Chinnakotla S, Radosevich DM, Dunn TB, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg. 2014;218:530–43.
55. Abu-El-Haija M, Nathan JD. Pediatric chronic pancreatitis: updates in the 21st century. Pancreatology. 2018;18:354–9.
56. Abu-El-Haija M, Anazawa T, Beilman GJ, et al. The role of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis: a report from the International Consensus Guidelines in Chronic Pancreatitis. Pancreatology. 2020;20:762–71.
57. Hackert T, Werner J, Weitz J, et al. Uncinate process first—a novel approach for pancreatic head resection. Langenbecks Arch Surg. 2010;395(8):1161–4.
58. Berger M, Bellin MD, Kirchner V, et al. Laparoscopic-assisted versus open total pancreatectomy and islet autotransplantation: a case-matched study of pediatric patients. J Pediatr Surg. 2020;55(3):558–63. pii: S0022–3468(19)30741–9.
59. Boggi U, Palladino S, Massimetti G, et al. Laparoscopic robot-assisted versus open total pancreatectomy: a case-matched study. Surg Endosc. 2015;29(6):1425–32.
60. Pulvirenti A, Pea A, Rezaee N, et al. Perioperative outcomes and long-term quality of life after total pancreatectomy. Br J Surg. 2019;106:1819.
61. Kneuertz PJ, Pitt HA, Bilimoria KY, et al. Risk of morbidity and mortality following hepatopancreatobiliary surgery. J Gastrointest Surg. 2012;16:1727–35.
62. Murphy MM, Knaus WJ II, Ng SC, et al. Total pancreatectomy: a national study. HPB. 2009;11:476–82.
63. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol. 2013;19:7258–66.
64. Grant CS, Van Heerden JA. Anastomotic ulceration following subtotal and total pancreatectomy. Ann Surg. 1979;190:1–5.
65. Scott HW Jr, Dean RH, Parker T, et al. The role of vagotomy in pancreaticoduodenectomy. Ann Surg. 1980;191:688–96.
66. Safioleas MC, Moulakakis KG, Andromanakos NP, et al. How necessary is vagotomy after pancreaticoduodenectomy and total pancreatectomy. Hepatogastroenterology. 2005;52:251–2.

Chapter 62
Open Distal Pancreatectomy for Pancreatic Cancer

Stefan Stättner, Florian Primavesi, David Fuks, and Kjetil Søreide

Take Home Messages

- For pancreatic cancer located in the body/tail an open resection is considered standard.
- Radical antegrade modular pancreatosplenectomy (RAMPS) may improve lymph node yield and R0 resections.

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- New onset diabetes is common after left resection, less so for exocrine insufficiency.
- Neoadjuvant treatment should be entertained for cancers with vessel involvement or locally advanced tumours.

Pearls and Pitfalls
- Experience with left resection is increasing due to broader indications also for benign and borderline lesions.
- In locally advanced cancers or cancers with vascular involvement, neoadjuvant treatment might increase survival and reduce postoperative fistula rates.
- Postoperative pancreatic fistula rates remain high independent of transection technique used.
- Indications for drains are more and more questioned, the final word on this topic is not set yet.

Future Perspectives
- Importance of extended resections, such as RAMPS procedures, remains to be proven.
- Randomised trials of (neo-)adjuvant therapy and body and tail cancers are needed.

62.1 Introduction

Cancer in the distal pancreas (left to the porto-mesenteric vein) may be considered for curative surgery. Only about 30% of pancreatic cancers arise in the body/tail region [1], and many may be unresectable at time of diagnosis due to the comparatively aggressive biology of distal tumours [2].

The practice of distal pancreatic resection demonstrates huge variation between regions, with several differences in type of access (open, laparoscopic and robotic), type of stump-handling and fistula mitigation strategies, and in type of patients (and lesions) found eligible for resection [3].

In this chapter we will discuss the open approach in distal resections as the most frequently used access technique for pancreatic cancer. Particular situations and techniques, such as distal pancreatectomy with coeliac-access resection for advanced disease are discussed elsewhere, as are the specific complications associated with pancreatic resections. Situations and technical details specific to distal pancreatectomy will be elucidated, where applicable, including the radical antegrade modular pancreato-splenectomy (RAMPS) technique.

62.2 Pre-Operative Evaluation

Several factors need to be considered in the pre-operative planning and decision-making which access to choose for resection. A high-quality tri-phasic CT scan is mandatory to evaluate the extent of the tumour—especially at the posterior margin—and the vascular characteristics. Tumour involvement of the splenic vein leading to peri-splenic varices or anatomical variants as the left hepatic artery arising from the left gastric artery are just some to be mentioned. In both cases, the surgical planning and approach to resection can be substantially affected. Discussion in a multidisciplinary team setting with dedicated specialists is recommended, especially for borderline lesions and cystic variants that warrant resection. Endoscopic ultrasound might be helpful in case a limited, parenchymal sparing resection is planned to better elucidate the future transection line. An important issue to be addressed are cancers with involvement of the splenic vessels, that would be in general be technically resectable with vascular resection, but where the questions remains if it is biologically plausible. There is no general agreement so far, which lesions are on the one hand technically well resectable but otherwise have biologically-wise a bad prognosis and might benefit from neoadjuvant treatment [4]. Trials are needed for this particular situation.

62.3 Technical Considerations

The principles for open and laparoscopic distal pancreatic resection are similar, but with some variation. In general, for cancer resection a combined pancreatosplenectomy is considered the standard treatment. William Mayo proposed the standard technique in 1913 which long set the standard for this rarely performed operation [5]. Detection rates of pancreatic lesions have increased steadily over the last years with better sonographic imaging, hence the numbers of distal pancreatic resection have increased substantially. This was accompanied by technical advancements, leading to wider use of minimally invasive techniques and consensus recommendations by international experts [6].

In cancer resection, aiming for tumour free margins is of utmost importance and key of all operative planning. Adequate lymph node dissection and avoidance or prediction of potential severe morbidity are further issues that need to be addressed preoperatively. The potential risks and benefits have to be outweighed against patient's needs and surgical experiences.

Several approaches for tumours of the body and tail of the pancreas have been described, but the so called radical antegrade modular pancreatosplenectomy (RAMPS) is probably the most debated. First described by Strasberg in 2003, this operation was adapted from the surgical oncological principles of pancreatoduodenectomy at that time [7]. High rates of R1 resections and early local and systemic recurrences were referred to the surgical approach, tackling the tumour from the left side by starting mobilising the spleen, making it difficult finding the way into the right plane and enabling early vascular control. Basically, the RAMPS approach starts dissecting from right to left, facilitating early central ligation of the splenic artery and vein, furthermore, integrating a proper central lymphadenectomy with clearance of lympho-vascular tissue alongside the celiac

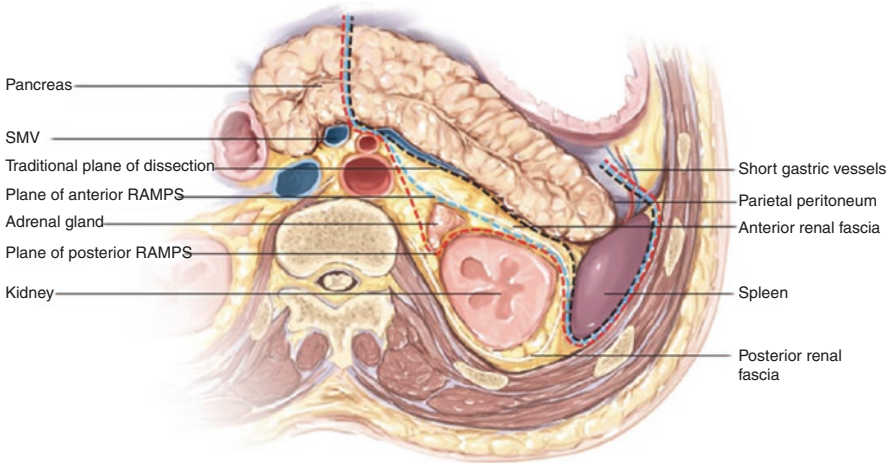

Fig. 62.1 Posterior anatomical planes guiding resection for RAMPS procedure. Transversal anatomical section depicting transection lines during 3 variants of distal pancreatic resection. Standard approach along Gerota's fascia (black broken line), anterior radical antegrade modular pancreatosplenectomy (blue broken line) and posterior radical antegrade modular pancreatosplenectomy (red broken line). (Reproduced from *Chun, YS. Role of Radical Antegrade Modular Pancreatosplenectomy (RAMPS) and Pancreatic Cancer, Ann Surg Oncol (2018) 25:46–50. 10.1245/s10434-016-5675-4. With permission of Springer*)

Table 62.1 Potential benefits and harms of RAMPS procedure [7–11]

Benefits	Harms
Early vascular control	Longer operating time
Improved visualisation of posterior planes	Higher complication rate
Higher lymph node yield	Prolonged recovery
Less tangential margin positivity	

trunk and the superior mesenteric artery. The landmark for further dissection is the left adrenal gland, respectively the left adrenal vein and the renal vein (Fig. 62.1). Tumours invading or coming close to Gerota's fascia, should be planned as a posterior RAMPS, including en bloc dissection of the left adrenal and pre-renal fat tissue. In smaller or anteriorly located lesions adrenalectomy needs to be avoided (anterior RAMPS). The left renal vein encounters the inferior border of the resection plane.

To date, no randomized controlled trial has proven an oncological benefit of the RAMPS technique compared to the conventional approach [8]. The potential benefits and harms are depicted in Table 62.1.

62.3.1 Approach to Open Resection

For open resections, a roof top incision is usually preferred as it gives good access to the left lateral and subcostal part of the abdomen, although some also use a standard midline incision [12]. Proper retraction is always mandatory to achieve a good

overview of the surgical field. A safe preparation being able to control essential vascular structures like the celiac trunk or the portal confluence at any time is highly recommended, especially in demanding borderline or locally advanced pancreatic cancers.

After proper exploration—the role of laparoscopy is discussed extensively elsewhere in this book—the gastrocolic ligament is either anatomically dissected off the transverse colon or transected to get into the Bursa omentalis (Fig. 62.2).

The anatomical preparation in planes allows to create a biologic vascularised tissue coverage with the omentum after resection has been performed. Regardless of the approach, careful preservation of the right gastroepiploic arcade must be pursued. The left colonic flexure is taken down and retracted caudally, while the stomach is explored and freed off adhesion to the pancreatic surface. There might be inflammatory adhesions that need careful evaluation to rule out any cancer invasion. In case of adjacent organ invasion, en bloc resection should be done for oncological safety (e.g. a wedge resection of stomach wall may be needed). For more disseminated involvement (e.g. seed-like dispersed nodules in the bursa omentalis) it may be advised to send specimen for frozen section and abort resection if malignancy is proven.

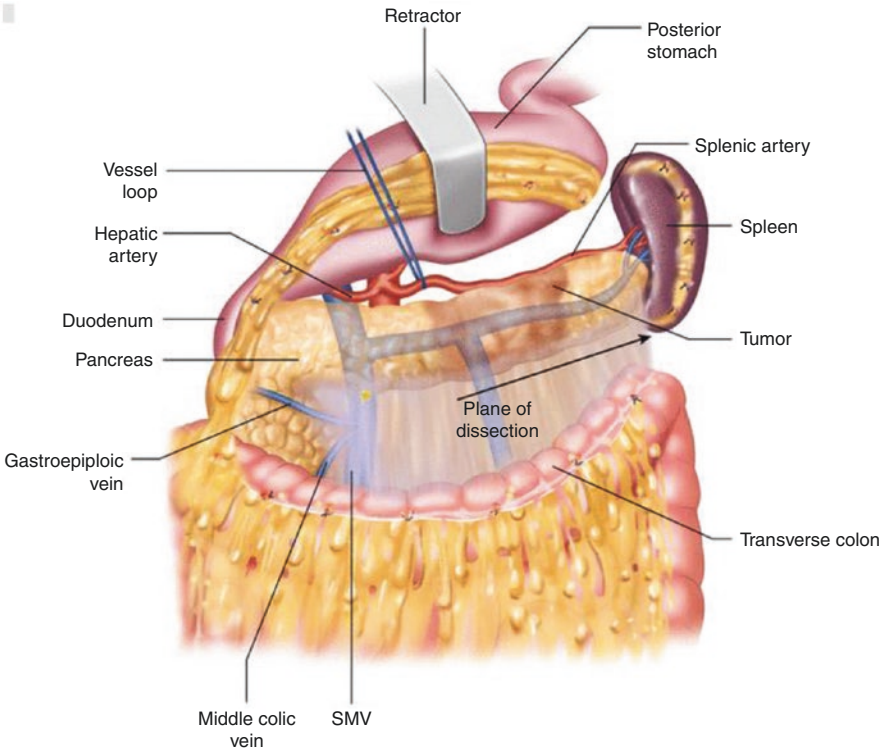

Fig. 62.2 Planes of dissection. Schematic overview of the original situs. To open the omental bursa, the gastrocolic ligament has to be divided. (*With permission of Springer*)

The pancreatic gland is now inspected, and the tumour explored. The lesser sac is opened close at its origin of the caudate lobe. Care has to be taken to avoid injury of a left hepatic artery arising from the left gastric artery.

The gastroepiploic vein is followed down to Henle's trunk and the superior mesenteric vein cranially freed of connective tissue. The neck of the pancreas can safely be lifted up off the portal vein confluence with a right-angled clamp and a loop pulled around to gently create traction and counter-traction. The caudal margin of the pancreas is further mobilised using energy devices like bipolar or ultrasonic shears, depending on the size and location of the tumour. Cancer at the inferior border of the body might invade the middle colic artery, this might be technically challenging but should be well distinguished on preoperative scans.

A lymphadenectomy is performed, starting at the left border of the hepatoduodenal ligament. The easiest and safest way is to dissect along the left hepatic artery, which has to be secured. Using vessel loops helps to create gentle traction and counter-traction and enhances the anatomical overview. Lymph nodes at the gastroduodenal artery should be included in the lymphadenectomy in cases with tumours located in the body of the gland. Posteriorly the portal vein is cleared off lymphovascular tissue and the left gastric vein (coronary vein) tied off at its inflow. At this stage, transection of the pancreas enables better access to the common hepatic artery and its central division towards the celiac trunk. Dividing the pancreas is clearly *a point of no return*, hence resectability needs to be proven before this step. When the gland has been divided, frozen sections of the margin should be sent. Various techniques of transection are reported, depending on the texture and the thickness of the gland (Table 62.2) [13].

Extended resections to the right might render sharp dissection and suture closure necessary. The splenic vein at its confluence is encircled with a loop and also checked for invasion. Any type of venous reconstruction might be feasible (direct closure, Patch or interposition graft, see chapter pancreatoduodenectomy with portal vein resection).

The splenic artery is carefully dissected and ligated with a double tie, leaving a 5 mm stump whenever feasible. Clamping before dissection adds to safety of this procedure, demarcation of the spleen will be nicely seen immediately. Ligating the artery before tying the vein avoids congestion of the spleen and surgical field, reduces blood loss and is therefore always recommended. Larger tumours of the body or stromal attachments might tackle this strategy in some cases. Lymphadenectomy should then be completed around the left gastric artery. The

Table 62.2 Transection techniques

Technique	Benefits	Potential risks/disadvantages
Stapled transection	Fast, safe, convenient	Costly
Electrocautery (±suture?)	Convenient, haemostasis	Duct closure sufficient?
Scalpel + suture	Less traumatic, cheap	Bleeding
Energy device[a] (±suture?)	Convenient	Duct closure sufficient?

[a]Ultrasonic shears or electrocautery shears such as Harmonic, Ligasure

coronary vein might be ligated or sealed for a second time at this anatomical level. In heavily obese patients, transection of the left gastric artery might be a technical option to provide a better lymphadenectomy, only for tumours of the body of the pancreas.

The splenic vein is now diverted using simple ties (Fig. 62.3). Care has to be taken to avoid stricture of the portal vein at the insertion site, hence for simple ties the stump needs a length of at least 5 mm. A Satinsky clamp can be used and a running suture applied for closure instead, or a vascular stapler. The inferior mesenteric vein can be either saved or also safely transected.

At this stage, complete vascular control is obtained, the last area where bleeding might occur are the short gastric vessels. At this point, a RAMPS procedure can be performed or a classical right to left approach handling along Gerota's fascia. In the latter case, the pancreas and spleen are lifted anteriorly, and the connective tissue is dissected with energy devices, ending with the splenic ligaments towards its backwards fixation. Finally, the short gastric vessels are divided. Care has to be taken to avoid decapsulation of the spleen and injury of the stomach, although the latter can be nicely over sewn or even wedge resected.

In larger tumours of the body, a RAMPS procedure is performed to gain better margins and increase the lymph node yield. After division of the splenic vein,

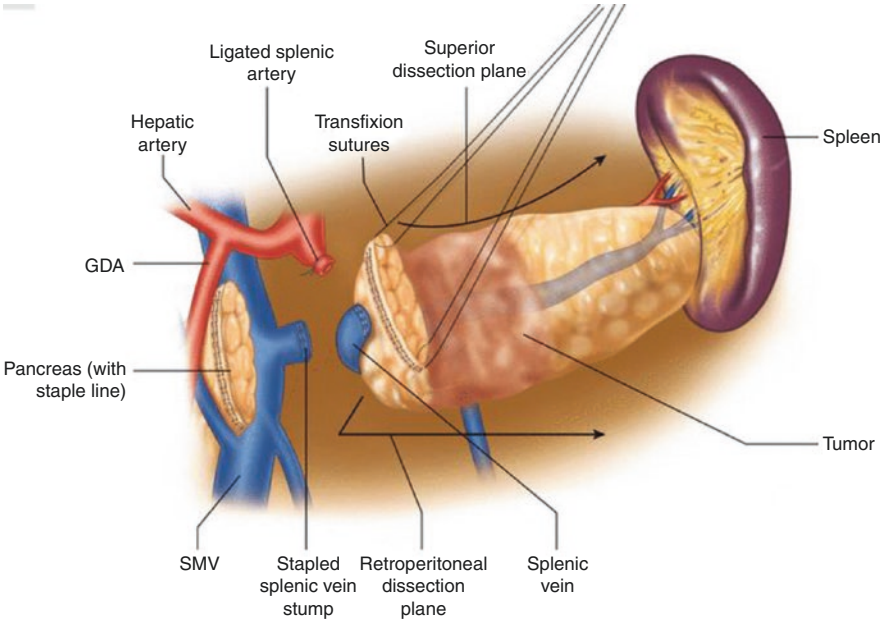

Fig. 62.3 Transection and central vascular ligation. Transection of the pancreas at the neck region offers best access as the parenchymal bridge is narrow and no major vessels appear. After stapler transection, which has to be done in one step using 1 cartridge, better access to ligate the central splenic artery and subsequently the splenic vein is possible. These procedures follow the same criteria for open and minimally invasive resections. (*With permission of Springer*)

dissection towards the superior mesenteric artery is mandatory and the tissue to the left of the artery is cleared. In such cases of larger tumours, an extensive Kocherization is helpful. At this step, the left renal vein as an important landmark should be transected freely as the inferior-posterior landmark of resection. Starting from medially, the adrenal vein needs to be visualised and a decision has to be made for either the anterior or posterior transection line. Cranially, the celiac trunk is cleared from connective, neuro- and lympho-vascular tissue on the left side accordingly making left diaphragmatic pillars visible. Gerota's fascia is completely resected together with prerenal fat. Transection of the short gastric veins enabling the stomach being retracted to the right is necessary at an earlier step of this complex procedure to facilitate a better view towards the cranio-posterior surgical field.

After removal of the specimen, a careful check of haemostasis and lymphatic leaks is mandatory. In any case of vascular reconstruction, the patency of the vessel needs to be finally evaluated. Final inspection of the stomach and transverse colon ends the procedure. If a surgical drain is used, it is usually inserted from laterally with the tip pointing at the pancreatic stump aiming for early removal. The colonic flexure is put back in its original position and the pancreatic stump carefully covered with the omentum or round ligament patch (Fig. 62.4) [14].

Special considerations have to be taken into account in locally advanced tumours encasing the celiac trunk and/or the superior mesenteric artery. Some major pitfalls can occur during surgery with potential life-threatening intraoperative complications. In Table 62.3 some scenarios and strategies are presented.

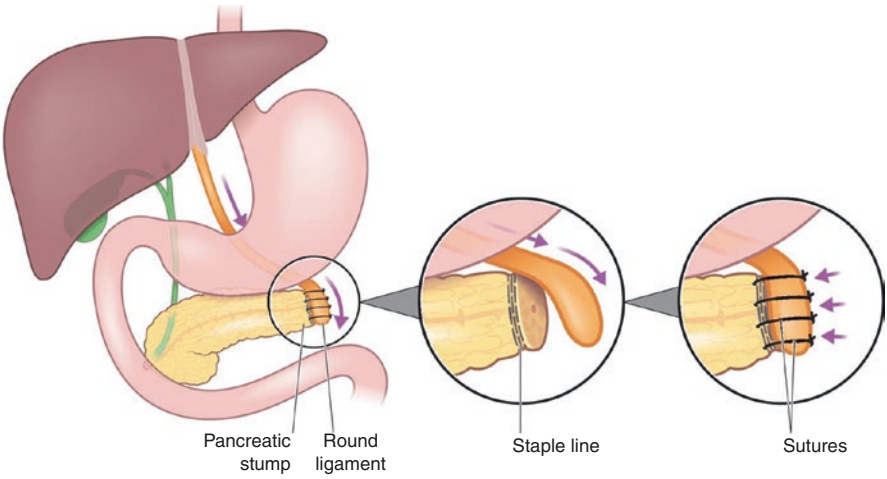

Fig. 62.4 Round ligament patch closure technique. The round ligament is mobilized behind the stomach and placed as coverage on to the pancreatic stump staple/suture line after distal pancreatectomy. The patch is then anchored on to the exposed pancreatic surface with sutures (distances are exaggerated for educational purposes). (Reproduced with permission from Br J Surg [14], Wiley ©2019)

Table 62.3 Difficult situations during resection, mainly for locally advanced tumours

Problem	Prevention	Potential solution
Bleeding from splenic artery during exploratory phase, e.g. in cases with short tumour-free distance due to encasement	• Get frozen section of perivascular tissue early, stop if invasive cancer is present • Sling celiac trunk and common hepatic artery • Keep the gastroduodenal artery safe • Have autologous material ready (testicular/ovaric vein) • Ask for help from experienced vascular surgeon	• Call for help from experienced colleague • Use local haemostatics • Controlled hypotension • Transect pancreas to gain better access • Try to clamp celiac trunk avoiding further vascular lesions, if not possible aortic clamping might be necessary • Try to dissect the tumour off, stop bleeding with suture even with minimum flow and reconstruct under better conditions
Bleeding from portal vein without previous control	• Meticulous dissection of all confluent branches • Vessel loops for immediate clamping • Transection of splenic artery before division of splenic vein	• Call for help of experienced surgeon • Use local haemostatic and local pressure • Clamp superior mesenteric artery and splenic artery to reduce backflow • If SMV is not accessible, perform Cattell-Braasch manoeuvre manually and use tourniquet for global flow control of SMV • Suture the leak to stop bleeding and proceed controlling confluence
Shrinking of mesocolon with adherence of middle colic artery	• Frozen sections to check for invasive cancer • Omit procedure if positive • Probatory clamping close at origin, further dissecting check closely	• Transect the artery at closest to origin (aim for R0)–Reconstruction is rather difficult and most likely not successful • Proceed with resection and check finally for ischemic bowel • Consider need for colectomy

62.3.2 Transection of the Pancreas and Handling the Stump

The main cause of morbidity after left resection is postoperative pancreatic fistula (POPF), a specific problem that is recognised worldwide and was dealt with in numerous studies. The risk of developing POPF is 20–35%, which is a considerable number [15]. Various techniques are in use; sharp knife dissection and suture, electrocautery, stapled transection and energy devices (Table 62.3). Minimally invasive approaches and the use of staplers have considerably added to the ongoing discussion. The International Study Group of Pancreatic Surgery (ISGPS) has recently published consensus guidelines on stump management [13]. The stump can be covered with biological tissue, e.g. the falciform ligament, or with bio-chemical agents, e.g. fibrin sealants, none has reduced rates of POPF and can therefore not be recommended [14, 16] (Fig. 62.5).

Table 62.4 Factors having potential impact on outcomes after pancreatic left resections

Patient related	Tumour/parenchyma related	Technique and perioperative treatment related
Gender	PDAC vs. other tumours	RAMPS vs. conventional resection
Age	Firmness of gland	Stump closure
Body mass index		Stump coverage
Immunosuppressive treatment		Surgical experience
Smoking		Somatostatin analogues
		Neoadjuvant treatment

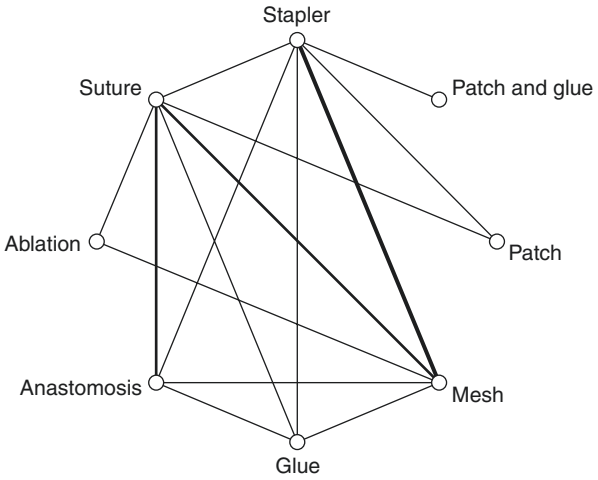

Fig. 62.5 Distal stump closure techniques. A network map showing correlation between all studies reviewed and outcomes compared. The thickness of the connecting lines indicates the number of direct comparisons. (Reproduced with permission from Br J Surg [14], Wiley ©2019)

62.4 Drains

Although many centres use surgical drains after distal pancreatectomy due to the high rate of clinically-relevant POPF, their routine application is still controversial [17]. A recent prospective, randomized, multicentre study comparing DPs with and without routine intraperitoneal drainage did not show any significant difference in POPF, severe complications or mortality. However, the group without drainage showed a significantly higher rate of intraabdominal fluid collection (22% vs. 9%) [18]. In a propensity-score matched study based on the American College of Surgeons-NSQIP database, routine drainage did actually increase the risk of POPF and overall morbidity [19]. There is also some retrospective data, that the type of drain also might influence the rate of POPF, with smaller drains reducing the degree

of suction on the pancreatic transection surface [20]. Furthermore, the timing of drain-removal is a subject of ongoing discussion. Some studies suggest, that removal as early as on the morning of the first postoperative day might be beneficial in patients with low risk of developing a clinically-relevant pancreatic fistula, and this could be facilitated by measuring drain-amylase and/or serum amylase [17, 21, 22].

62.5 Perioperative Outcomes

Perioperative morbidity might be influenced by several factors that are either patient related, tumour and/or parenchyma related or related to the techniques used (Table 62.4).

The most specific complication after pancreatic left resection is postoperative pancreatic fistula [23]. Up to one third of patients (25–35% [15]) develop leakage of the stump, which affects the further postoperative course and has economic impact as well. Furthermore, POPF may lead to accumulation or be causative for other specific complications as delayed gastric emptying, haemorrhage or chyle leaks as well as collections, abscesses or wound infections.

The randomized controlled DISPACT trial was performed in 21 European centres and compared stapler versus hand-sewn closure [24]. The 30-day fistula rate in 352 analysed patients was 36%, among which 56% were clinically relevant. 30 and 90-days mortality was 1 and 3% respectively. 11% of patients developed new onset diabetes.

Neoadjuvant chemotherapy might have an impact on postoperative POPF and reduce the risk significantly, in a Propensity-score-matched cohort analysis of 188 patients, POPF was reduced to 10% (vs. 23%) after neoadjuvant chemotherapy [4].

All patients should be run under evidence based enhanced recovery programs (ERAS), which have recently been updated for pancreatic surgery [25]. Adherence to an ERAS protocol is able to reduce non-surgical complications like venous thromboembolism, pneumonia or catheter and line associated sepsis.

62.5.1 Endocrine and Exocrine Functional Outcomes

New onset diabetes after left resection can be found in 14–28% of patients in the short term and up to 36% in the long term. Patients suffering from diabetes preoperatively are very likely to develop insulin dependency [26, 27]. There is a correlation of resected volume and glucose tolerance. The exocrine function is impaired in the early postoperative period in 18–80% (depending on the method of testing). It is important to take preoperative function into account, which can be reduced by tumour induced obstructive pancreatitis and loss of acinar cells [28].

62.6 Conclusions

Distal resection of the pancreas remains a challenging procedure which is recently increasingly performed due to earlier recognition of premalignant and cystic lesions. The cornerstone of resection for ductal adenocarcinomas remains a negative margin and an adequate lymph node dissection. While the radical antegrade modular pancreatosplenectomy (RAMPS) has influenced the open approach and led to ongoing discussions among pancreatic surgeons worldwide, minimally invasive resections are clearly on the rise. While early recovery seems clearly beneficial for the laparoscopic approach, the oncological benefits remain to be proven with well-designed randomized studies. Education and training to gain proficiency in this technique remains a challenge.

References

1. van Erning FN, Mackay TM, van der Geest LGM, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol. 2018;57:1655–62.
2. Dreyer SB, Jamieson NB, Upstill-Goddard R, et al. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br J Surg. 2018;105:e183–91.
3. Maggino L, Malleo G, Salvia R, et al. Defining the practice of distal pancreatectomy around the world. HPB (Oxford). 2019;21:1277–87.
4. Lof S, Korrel M, van Hilst J, et al. Impact of neoadjuvant therapy in resected pancreatic ductal adenocarcinoma of the pancreatic body or tail on surgical and oncological outcome: a propensity-score matched multicenter study. Ann Surg Oncol. 2020;27:1986–96.
5. Mayo WJ. I. the surgery of the pancreas: I. injuries to the pancreas in the course of operations on the stomach. II. Injuries to the pancreas in the course of operations on the spleen. III. Resection of half the pancreas for tumor. Ann Surg. 1913;58:145–50.
6. Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami international evidence-based guidelines on minimally invasive pancreas resection. Ann Surg. 2020;271:1–14.
7. Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery. 2003;133:521–7.
8. Chun YS. Role of radical Antegrade modular Pancreatosplenectomy (RAMPS) and pancreatic cancer. Ann Surg Oncol. 2018;25:46–50.
9. Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg. 2007;204:244–9.
10. Grossman JG, Fields RC, Hawkins WG, Strasberg SM. Single institution results of radical antegrade modular pancreatosplenectomy for adenocarcinoma of the body and tail of pancreas in 78 patients. J Hepatobiliary Pancreat Sci. 2016;23:432–41.
11. Sivasanker M, Desouza A, Bhandare M, et al. Radical antegrade modular pancreatosplenectomy for all pancreatic body and tail tumors: rationale and results. Langenbecks Arch Surg. 2019;404:183–90.
12. Andren-Sandberg A, Wagner M, Tihanyi T, et al. Technical aspects of left-sided pancreatic resection for cancer. Dig Surg. 1999;16:305–12.
13. Miao Y, Lu Z, Yeo CJ, et al. Management of the pancreatic transection plane after left (distal) pancreatectomy: expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2020;168:72–84.

14. Ratnayake CBB, Wells C, Hammond J, et al. Network meta-analysis comparing techniques and outcomes of stump closure after distal pancreatectomy. Br J Surg. 2019;106:1580–9.
15. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161:584–91.
16. Uemura K, Satoi S, Motoi F, et al. Randomized clinical trial of duct-to-mucosa pancreaticogastrostomy versus handsewn closure after distal pancreatectomy. Br J Surg. 2017;104:536–43.
17. Seykora TF, Liu JB, Maggino L, et al. Drain management following distal pancreatectomy: characterization of contemporary practice and impact of early removal. Ann Surg. 2019. Publish Ahead of Print.
18. Van Buren G II, Bloomston M, Schmidt CR, et al. A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. Ann Surg. 2017;266:421–31.
19. Behrman SW, Zarzaur BL, Parmar A, et al. Routine drainage of the operative bed following elective distal pancreatectomy does not reduce the occurrence of complications. J Gastrointest Surg. 2015;19:72–9; discussion 79.
20. Dokmak S, Fteriche FS, Meniconi RL, et al. Pancreatic fistula following laparoscopic distal pancreatectomy is probably unrelated to the stapler size but to the drainage modality and significantly decreased with a small suction drain. Langenbecks Arch Surg. 2019;404:203–12.
21. Adachi T, Kuroki T, Kitasato A, et al. Safety and efficacy of early drain removal and triple-drug therapy to prevent pancreatic fistula after distal pancreatectomy. Pancreatology. 2015;15:411–6.
22. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg. 2010;252:207–14.
23. Soreide K, Healey AJ, Mole DJ, Parks RW. Pre-, peri- and post-operative factors for the development of pancreatic fistula after pancreatic surgery. HPB (Oxford). 2019;21:1621–31.
24. Diener MK, Seiler CM, Rossion I, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet. 2011;377:1514–22.
25. Melloul E, Lassen K, Roulin D, et al. Guidelines for perioperative care for pancreatoduodenectomy: Enhanced Recovery After Surgery (ERAS) recommendations 2019. World J Surg. 2020;44(7):2056–84.
26. Kang JS, Jang JY, Kang MJ, et al. Endocrine function impairment after distal pancreatectomy: incidence and related factors. World J Surg. 2016;40:440–6.
27. De Bruijn KM, van Eijck CH. New-onset diabetes after distal pancreatectomy: a systematic review. Ann Surg. 2015;261:854–61.
28. Beger HG, Mayer B. Early postoperative and late metabolic morbidity after pancreatic resections: an old and new challenge for surgeons—a review. Am J Surg. 2018;216:131–4.

Chapter 63
Laparoscopic Distal Pancreatectomy

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Take Home Messages
- Laparoscopic distal pancreatectomy has comparable short-term outcomes to open resection in favour of shorter hospital stay with laparoscopy.
- Same surgical oncological principles should apply for open or laparoscopic distal resections for malignant lesions.
- Post-operative pancreatic fistulae remains one of the most frequent complications.

Pearls and Pitfalls
- In premalignant lesions (e.g. pancreatic cysts) it is debated if a splenectomy is truly mandatory.
- Laparoscopic access should not be an excuse to resect more lesions just for being minimal-invasive—same indications apply as for open surgery.
- No specific technique has demonstrated superior ability to reduce post-operative fistulae.
- In pancreatic cancer, a non-inferior effect of laparoscopic to open access on oncological outcomes remains to be proven.

Future Perspectives
- Ongoing randomized trials will investigate effect on oncological outcomes, particularly long-term survival.
- Importance of extended resections, such as RAMPS procedures, remains to be proven.
- Added value of robotic surgery (over laparoscopy) to open surgery remains unclear.

63.1 Introduction

Many lesions in the pancreas are increasingly detected as incidental findings on imaging performed for other reasons. These may range from benign cystic lesions to cysts of indeterminate nature, to non-functional neuroendocrine tumours or suspected pancreatic cancers. Hence, lesions in the distal pancreas (left to the portomesenteric vein) are increasingly considered for surgery. Only about 30% of pancreatic cancers arise in the body/tail region [1], and many may be unresectable at time of diagnosis due to the comparatively poor and aggressive biology of distal tumours [2].

The practice of distal pancreatic resection demonstrates huge variation between regions, with several differences in type of access (open, laparoscopic and robotic),

type of stump-handling and fistula mitigation strategies, and in type of patients (and lesions) found eligible for resection [3].

In this chapter we will discuss distal resections for premalignant conditions (usually cysts) and current data available for pancreatic cancer. We will discuss factors relevant to the laparoscopic approach (but not robotic) with technical considerations and associated outcomes.

63.2 Pre-Operative Evaluation

The indication for surgery should be based on clinical evaluation and work-up, and independent of the surgical approach. Once the decision to proceed with pancreatectomy is made, several factors need to be considered (Box 63.1) in the pre-operative planning to choose the approach for the resection [4].

Box 63.1 Factors to be evaluated for patient selection when considering surgical access

Surgeon-related factors	• Surgeon experience (lap and open) • Team experience
Patient-related factors	• General health and comorbidities • Previous abdominal surgery • Body habitus; BMI/fat distribution • Preoperative diagnosis
Procedure-related factors	• Visualization by MIS vs. open • Wound issues • Adequate surgical equipment
Tumour-related factors	• Benign vs. malignant • Size • Localization, anatomical variants • Locally advanced? Organs involved?
Societal and health economic factors	• Cost of procedure • Return to work • Quality of life

63.3 Technical Considerations

The principles for open and laparoscopic distal pancreatic resection are similar, but with some variation related to the specific access used. Several variations and preferences to port placement, equipment and nuances to various steps exist between surgeons and institutions.

63.3.1 Patient Positioning and Port Placement

Patient positioning is variable, depending on equipment available. In general, positioning should facilitate access to the left flank, provide a gravitational effect on the intestines to improve access and should keep in mind the position on the table in case of need to convert to open surgery.

The surgeon and assisting surgeon (controlling the camera) may stand on the patient's right side. Some prefer a supine split-leg position which is ideal for a right to left dissection while most prefer a right lateral decubitus or at least a 45° elevation of the left flank which is the preferred position for a left to right dissection.

A right lateral decubitus position is used by some, others use a pillow under the left flank and position the table in a tilt (head up, left flank up) to facilitate a similar effect (given the OR table as the operational function to do this).

Several variations and preferences to port placement, equipment and nuances to various steps exist between surgeons and institutions. Patient's BMI, body habitus and previous surgeries may also play a role in adjusting port placements. A setup for port placement is suggested in Fig. 63.1. Four trocars placed with one above the umbilicus (12 mm); one in the lateral part of the left rectus abdominis muscle (12 mm); one to the left of the xiphoid process (5 mm); and one in the left flank (5 mm). Additional ports may be placed as needed and should be used liberally to facilitate access and avoid conversion, if possible. Several techniques are used to remove the stomach away from the field, either by suturing to the abdominal wall, lift by a tape/sling, use of retractor (e.g. Nathasons's retractor) or simple lift by a grasper handled by a second assistant (which may standing at patient's left side).

A standardised approach to laparoscopic distal pancreatectomy has been proposed by the 'clockwise, stepwise' approach [6, 7] (Fig. 63.2). The left colonic flexure will be mobilized (Fig. 63.2, Step 1), and the splenocolic ligament will be

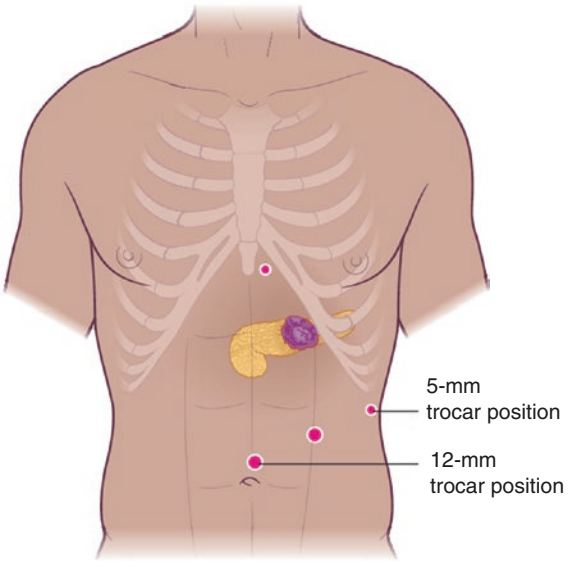

Fig. 63.1 Suggested placement of trocars for laparoscopic distal pancreatectomy. (Reproduced from Björnsson et al. [5]. © *2020 The Authors. British Journal of Surgery published by John Wiley & Sons Ltd on behalf of BJS Society Ltd*)

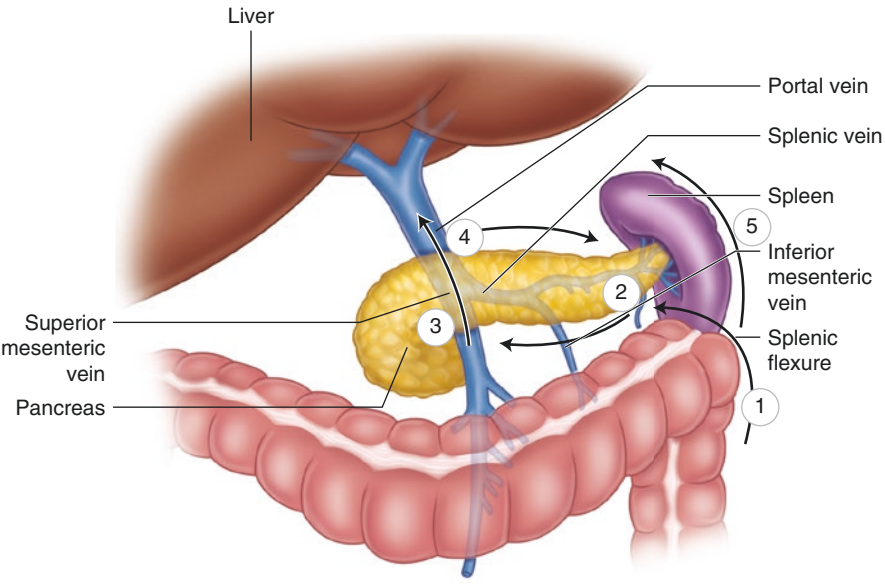

Fig. 63.2 The stepwise, clockwise approach to laparoscopic distal resection. The five clockwise steps as suggested by Asbun and Stauffer [6]. The 5 steps are indicated by numbered circles. (1) mobilize the splenic flexure of the colon; (2) dissect the inferior border of the pancreas; (3) undermine the pancreas at the intended level of transection; (4) identify the splenic artery and secure & ligate before transecting the pancreas; (5) mobilization of the spleen, ±splenectomy. For details, please refer to main body of text

divided. Thereafter, the omental bursa will be opened, and the stomach completely mobilized, including the short gastric vessels. The lesion in the pancreas will be identified with or without the help of ultrasonography. The inferior border of the pancreas will be dissected, and a band placed around the pancreas between the lesion and spleen if appropriate (**Step 2**). A band (a penrose drain; a vascular sling or similar) may be placed around the pancreas to the right of the lesion (and the splenic vein, if splenectomy is intended). The pancreas may be undermined at the level of the portomesenteric confluence in case of a more proximal located lesion (**step 3**). Before dividing the pancreas, the splenic artery will be identified and secured (**step 4**) using Hem-o-lock clips (Teleflex Medical, Weck Drive, Research Triangle Park, NC, USA). In cases of spleen-preserving procedures, the splenic artery will be dissected from the pancreas and left intact. To improve visibility of the superior border of the pancreas, the stomach may be sutured to the anterior abdominal wall or, lifted by an assistant.

Depending on the preoperative assessment, lymphadenectomy will be performed as indicated for pancreatic adenocarcinoma. The pancreas will be divided using a linear stapler with a cartridge size fitting the thickness of the pancreas (Fig. 63.3). It is the author's personal preference is to use a large, black load with enforcement of the stapler line. However, we recognize the data regarding use of stapler with and

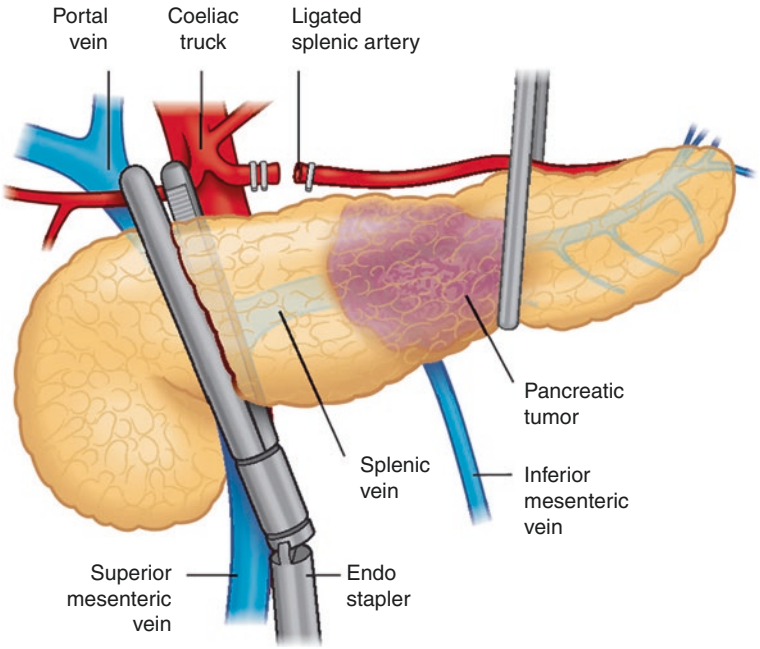

Fig. 63.3 Division of the gland by using a stapler. Performing a subtotal distal resection may be required of the lesion is close to the portomesenteric vein, the gland is then transected at the portomesenteric confluence (the pancreatic neck), otherwise the transection can be performed more distally for lesions located in the body or tail of the pancreas. (Reproduced with permission from Björnsson et al., Br J Surg [5] by Wiley, copyright the Authors © 2020)

without enforcement or other techniques is debated [8–12]. Notably, a randomised trial found no differences in complications (including post-operative fistulae rate) with use of enforced compared to bare staplers [13]. A systematic review suggested staplers to be superior over suture closure of the stump with regard to fistula rates [14], but the data were likely skewed towards open resections with uncertainty of how this would fare for laparoscopic resections. Overall, there are numerous variations and techniques reported, but systematic reviews [15] and consensus data currently does not support one over another [16].

A gradual stepwise compression technique and division is used before firing the stapler [7]. This standardized approach to laparoscopic distal resection, with stepwise graded compression technique for pancreatic transection has been described to reduce the risk of rupture of the pancreas along the stapling line [6, 7]. While the stapler size to pancreas thickness ratio may be of some importance [17], it is recognized that not all glands will fit with the staplers available and hence universal recommendations may not apply [16].

Following division of the pancreas, the resection will be performed in a medial to lateral direction (**step 4**). Lastly (**step 5**), mobilization of the spleen is done (in case splenectomy en-bloc is included as part of the procedure). The surgical specimen will be placed in a plastic bag and retrieved through enlargement of the trocar incision—either in the midline or, as some prefer, through a Phannenstiel incision over the symphysis pubis.

A drain may be placed depending on surgeon preference and local practice, although the role of drains in pancreatectomy remains debated [15, 18–20]. Early removal of drain is usually practiced, depending on the character and amount of drainage reflected by the amylase levels.

63.4 The Lateral Approach

For lesions located more distal in the pancreatic gland, an alternative to the 'clockwise' or 'medial approach' may be entertained, and a 'lateral approach' has been described [21] (Fig. 63.4). This technique may facilitate spleen-preservation.

63.5 Spleen Preservation or Splenectomy with Distal Pancreatectomy

The role of spleen preservation is much debated. Considerable variation exists in practice across centers [22]. Splenectomy is regarded as part of an oncological procedure in case of confirmed or suspected malignancy, although the exact role of lymph node dissection and inclusion by splenectomy remains to be debated. One study found an overall low involvement, and no positive lymph node in station 10 (splenic hilum) when tumour was located in the pancreatic body, rather than tail, and when no suspected lymph nodes found on CT [23].

For lesions not showing an overt malignant character, it is generally recommended to preserve the spleen, if possible. Avoiding splenectomy is associated with fewer complications and lower risk for surgical site infections [24, 25] but not in all studies [26]. Smaller lesions are associated with a higher chance for successful spleen-preserving procedure [27, 28].

Two types of techniques for spleen preservation are described, the Kimura technique [29] and Warshaw technique [30]. The Kimura procedure preserves the splenic vessels by an accurate dissection and ligation of small splenic branches and splenic vessels away from the pancreas. The Warshaw technique leaves the spleen to be perfused by the short gastric artery and the left gastroepiploic artery, dissecting

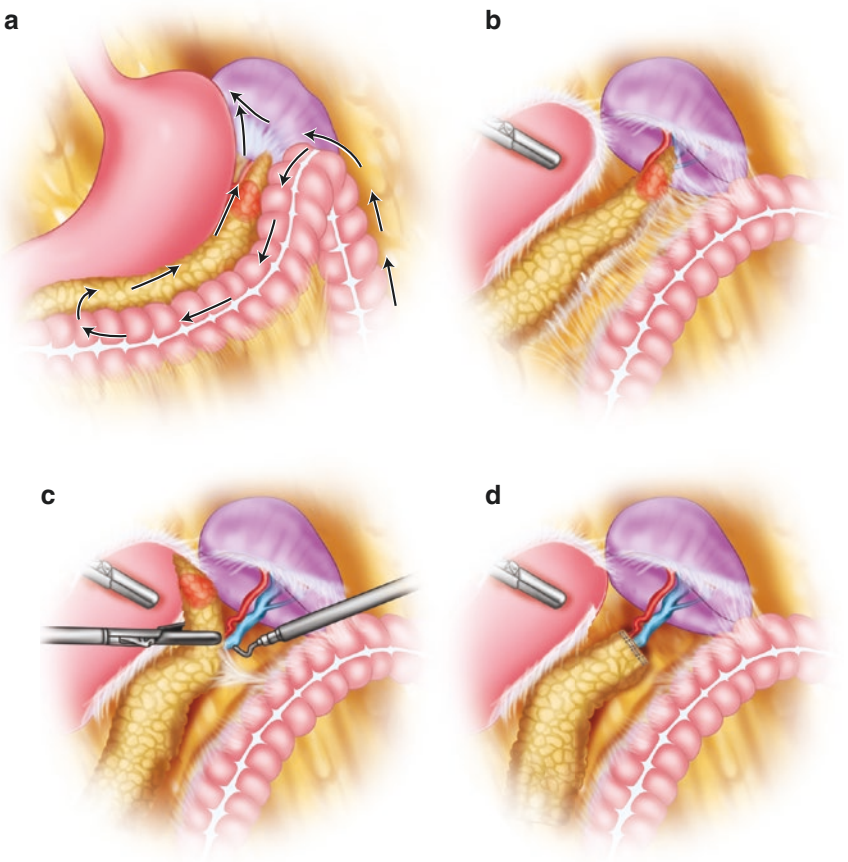

Fig. 63.4 The lateral approach to distal pancreatectomy. Steps to lateral distal pancreatectomy. The inferior and superior borders of the pancreas are identified (**a**, **b**) and the distal gastric vessels are identified and the lesser sac is entered. The pancreas is elevated from the splenic vessels (**c**) in a lateral to medial manner, for a spleen-preserving procedure. When well medial to the lesion (**d**), the pancreas is transected using a laparoscopic stapler. Further details and instructional videos are provided in. (Reproduced with permission from Stricland et al. [21], Surgical Endoscopy, Springer ©2015)

the splenic vessels at the transection level of the pancreas and the splenic hilum. Both these procedures are described as safe and feasible.

Robotic laparoscopic distal pancreatectomy is even less widespread in use than laparoscopic resections. However, outcomes appear to be overall similar, with a higher spleen-preservation rate for robotic resections [31]. This latter effect may be attributed to a better technical control and handling with the 3-dimensional space-handling by the robotic platform, but may also be attributed to selection of cases for robotics in the early phases of implementation of this technique. Further comparative data are needed.

63.6 Complications

Complications encountered after distal pancreatectomy are the same as those for pancreatic head resections [24, 32, 33], and defined by the consensus groups for postoperative pancreatic fistulae, delayed gastric emptying, and chyle-leak (as covered elsewhere in this book). However, while fistulae rates may be higher in distal resections (up to 30%), they are usually less severe and have much less grave consequences. Also, mortality is usually much lower after distal resections (at 1%) compared to pancreatic head resections (mortality usually reported between 3–5%) [34–37], most likely explained by a less invasive procedure and lower risk for severe complications.

63.7 Effect on Short-Term Outcomes

Several observational studies report on beneficial short-term effect of laparoscopic distal resections compared to open. Less bleeding, less morbidity and shorter hospital stay is consistently reported across reports [4].

In the randomized LEOPARD trial, [37] the laparoscopic approach reduced time to functional recovery compared with open distal resections. Notably, while the overall rate of complications was not reduced, the use of minimal invasive access was initially associated with less delayed gastric emptying and better quality of life without increasing short-term costs [37]. However, upon 1-year follow up, the costs, quality of life and cosmesis results became comparable between the two groups [38]. Long-term oncological outcomes are still awaited from this trial.

In the more recent LAPOP trial [5] comparing laparoscopic and open distal pancreatectomy, median hospital stay was shorter, time to functional recovery was shorter, and less bleeding was observed in the laparoscopic group. Of note, most of the lesions included where of benign or cystic origin, with no extrapolation possible to malignant lesions or large tumours.

The short-term benefits of laparoscopic distal resections has also been shown in observational studies [22, 36], reporting overall variation between regions but in general laparoscopy is associated with almost 50% reduction in length of stay compared to open surgery [39]. However, readmissions are quite common, with up to 20% in some series [36], and may be due to early discharge or late presentation of complications (e.g. pancreatic fistulae) that emerge only after patients have been discharged.

63.8 Use and Implementation of Open Versus Laparoscopic Access for Distal Pancreatectomy

Regional variation is considerable in the use of minimal-invasive access (most often laparoscopy) and the take-up rate is now around 46% in a multicentre study from the UK representing ‘early adopters’ to laparoscopic distal resections [40],

over 60% laparoscopy rate in a nationwide study from Norway [36] including all centers and all patients, but with notable variation between regions in the adoption of laparoscopy (15% in the lowest to 80% in the highest rate) [22]. In the US, adoption of laparoscopic distal pancreatectomy has been slow [41]. Training and access to minimal invasive surgery and particular HPB is an issue that is not easily overcome nor have a universal answer [42]. Training programmes, curricula and guidelines have been proposed in an attempt to standardize common themes of training and education as well as practice of minimal-invasive pancreatic surgery [43, 44].

63.8.1 Learning Curve and Volumes

Training programs for minimally invasive distal pancreatectomy, laparoscopic pancreatoduodenectomy and robotic pancreatoduodenectomy have been described with acceptable outcomes during the learning curve and improved outcomes after training [45]. Learning curve studies have revealed an association between growing experience and improving perioperative outcomes, with cut-off found at around 30 procedures in one study [40]. In addition, the association between higher center volume and lower mortality and morbidity has been reported by several studies, suggesting an effect of centralization of procedures [32], while others have suggested that this would have no effect [46].

63.8.2 Difficulty Scores

Agreed and universal methods for scoring difficulty and evaluation of laparoscopic distal pancreatectomy do not exist, although some scores are proposed [47, 48]. The Japanese classification system [47] (Figs. 63.5 and 63.6) for difficulty of laparoscopic distal pancreatectomy is currently the best standardized system, with good outcomes and robustness reported in an external validation cohort [49].

63.9 Oncological Outcomes for Open Vs. Laparosopic Distal Pancreatectomy

While both RCTs (LEOPARD, LAPOP) discussed above prove the short-term benefits of laparoscopy, there are no randomised data regarding oncological outcomes. Adhering to oncologic resection principles is as crucial laparoscopically as in open surgery. Any safe oncologic techniques should aim for R0 resection for curative-intent and sufficient nodal harvest for accurate staging, keeping in mind the

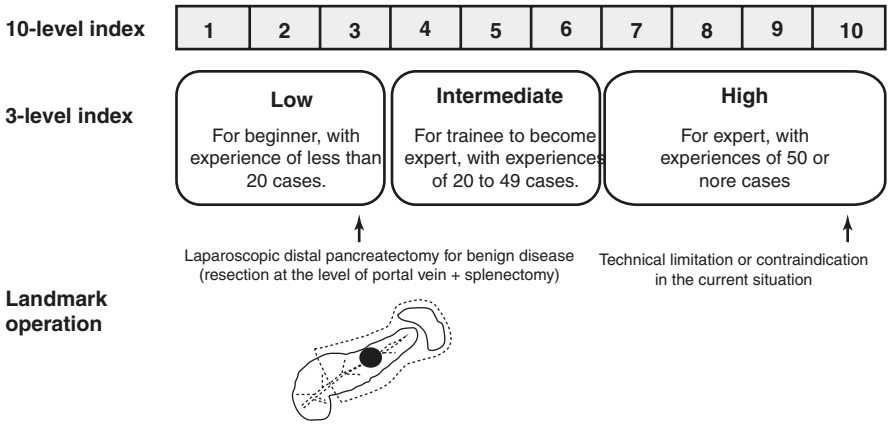

Fig. 63.5 Difficulty index of laparoscopic distal pancreatectomy. According to 10-level difficulty index, index 1 and 10 were defined as the easiest and the most difficult cases, respectively. Difficulty was also classified into three indexes in the viewpoints of education; low (1–3, for beginner), intermediate (4–6, for trainee to become an expert), and high (7–10, for expert). As a landmark operation, laparoscopic distal pancreatectomy with splenectomy for benign disease by the resection line at portal vein was set at index 3 to share the common scale of difficulty index among operators and reviewers. Scoring of likely difficulty of laparoscopic distal pancreatectomy. (Reproduced with permission from [47] from Wiley © 2018)

Type of operation	Score
DP-S for benign disease	+1
SPDP	+3
RAMPS	+4

Pancreatic resection line	Score
Portal vein level	+1
Pancreatic tail	0

Tumor close to major vessel[a]	Score
Presence	+2
Absence	0

Tumor extension to peripancreatic tissue	Score
Presence	+1
Absence	0

Left side portal hypertension and/or splenomegaly	Score
Presence	+5
Absence	0

Fig. 63.6 Difficulty scoring system for laparoscopic distal pancreatectomy. The difficulty index is calculated by the addition of factors including type of operation, resection line of the pancreas, presence or absence of the tumor close to the major vessels, tumor extension to peripancreatic tissue, and left side portal hypertension and/or splenomegaly. [a]The situations include that the tumor abutment to the splenic artery/vein is observed during SPDP, the tumor invasion is noted near the confluence of the splenic vein and superior mesenteric vein, or tumor is close to the root of splenic artery. *DP-S* distal pancreatectomy with splenectomy, *RAMPS* radical antegrade modular pancreatosplenectomy, *SPDP* spleen and vessel preserving distal pancreatectomy. (Reproduced from [47] with permission from Wiley and Sons © 2018)

limitations of staging for biological behaviour of tumours [50]. The R0-criteria is similar for body and tail cancers [51] to those applied for head of pancreas malignancies. The often reported poorer outcomes in pancreatic body and tail cancers is most likely due to a commonly late presentation and possibly more advanced biology, as these cancers have a higher rate of squamous subtypes and aggressive behaviour [2]. Cancer of the body and tail should be approached by a multimodal approach [52], considering neoadjuvant therapy as part of the management plan before surgery [53, 54] regardless of mode of access for surgery.

Systematic review and metanalysis [55–57] comparing the oncological safety of open to laparoscopic distal resections find that there are overall short-term benefits with laparoscopy, including less blood loss, lower morbidity and shorter hospital stay, but notably no hard data on cancer outcomes are reported. One meta-analysis calculated no significant difference in the 3-year (HR 1.03, 95% CI 0.89–1.21; P = 0.66) and 5-year overall survival (HR: 0.91, 95%CI 0.65–1.28; P = 0.59) [56]. Another systematic review found that laparoscopic (or minimal invasive access) was associated with comparable survival, R0 resection, and use of adjuvant chemotherapy, but a lower lymph node yield, as compared to open distal resection [57]. However, there are caveats in the comparisons between laparoscopic and open resections. For one, tumours were found to be of smaller size in the laparoscopic distal resection group in two of the metanalyses, [55, 57] with lower lymph node yield with laparoscopic access [57]. Therefore, due to treatment allocation bias and lower lymph node yield the oncologic efficacy of minimal-invasive distal pancreatectomy remains uncertain.

63.9.1 Minimal-Invasive Radical Antegrade Modular Pancreatosplenectomy (RAMPS)

The RAMPS procedure was designed to achieve optimall radicality for pancreatic cancer lesions in the body and tail. The details are discussed more extensively in the chapter on “open distal pancreatectomy” in this book. Several reports have emerged with the use of laparoscopic RAMPS and more recently with use of robotic-assisted technique [58–63]. data are scarce on the a exact role of this technique for cancer outcomes, independent on acces modality. A randomised trial has been designed to compare robotic RAMPS to a standard resection [64]. However, the endpoints (primary endpoint is R0 rate; secondary endpoints are the number of harvested lymph nodes, perioperative complications and perioperative indicators such as duration of surgery, blood loss, blood transfusion volume, costs) will not allow for evaluation of the actual impact on cancer survival.

A video showing a laparoscopic RAMPS procedure is presented (Video 63.1; courtesy Fuks & Gayet), which nicely demonstrates the principles and technique when this procedure is done.

63.10 Costs

As part of the potential benefits and also downsides to laparoscopic distal pancreatectomy is the cost-effectiveness aspect, another debated topic in this regard [38, 65–69]. The debate includes a higher procedure cost based on equipment, yet a potential cost-saving on the side of hospital days. Health care systems, insurance coverage, out of pocket costs and financial incentives may influence how this is valued overall. The randomised LEOPARD trial suggest that laparoscopy was at least as cost effective as open distal resection [38].

63.11 Conclusions

Laparoscopic distal pancreatectomy is safe, effective and comparable with the outcomes of open approach despite limited randomized controlled trials. Long-term oncologic outcomes remain to be proven for malignant lesions. Training and standardized approach to laparoscopic distal pancreatectomy suggest an improvement in learning curve while indications to perform an open or laparoscopic approach depends on several factors including surgeon experience, patient and tumour related factors. Finally, oncologic principles in distal pancreatectomy for pancreatic tail tumours must be maintained whether approach is open of laparoscopic.

References

1. van Erning FN, Mackay TM, van der Geest LGM, Groot Koerkamp B, van Laarhoven HWM, Bonsing BA, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol. 2018;57(12):1655–62. https://doi.org/10.1080/0284186x.2018.1518593.
2. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ, Biankin AV, et al. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br J Surg. 2018;105(2):e183–e91. https://doi.org/10.1002/bjs.10772.
3. Maggino L, Malleo G, Salvia R, Bassi C, Vollmer CM Jr. Defining the practice of distal pancreatectomy around the world. HPB (Oxford). 2019;21(10):1277–87. https://doi.org/10.1016/j.hpb.2019.02.016.
4. Rosok BI, de Rooij T, van Hilst J, Diener MK, Allen PJ, Vollmer CM, et al. Minimally invasive distal pancreatectomy. HPB (Oxford). 2017;19(3):205–14. https://doi.org/10.1016/j.hpb.2017.01.009.
5. Björnsson B, Larsson AL, Hjalmarsson C, Gasslander T, Sandström P. Comparison of the duration of hospital stay after laparoscopic or open distal pancreatectomy: randomized controlled trial. Br J Surg. 2020. https://doi.org/10.1002/bjs.11554
6. Asbun HJ, Stauffer JA. Laparoscopic approach to distal and subtotal pancreatectomy: a clockwise technique. Surg Endosc. 2011;25(8):2643–9. https://doi.org/10.1007/s00464-011-1618-0.
7. Asbun HJ, Van Hilst J, Tsamalaidze L, Kawaguchi Y, Sanford D, Pereira L, et al. Technique and audited outcomes of laparoscopic distal pancreatectomy combining the clockwise approach,

progressive stepwise compression technique, and staple line reinforcement. Surg Endosc. 2020;34(1):231–9. https://doi.org/10.1007/s00464-019-06757-3.
8. Pulvirenti A, Landoni L, Borin A, De Pastena M, Fontana M, Pea A, et al. Reinforced stapler versus ultrasonic dissector for pancreatic transection and stump closure for distal pancreatectomy: a propensity matched analysis. Surgery. 2019;166(3):271–6. https://doi.org/10.1016/j.surg.2019.02.016.
9. Nishikawa M, Yamamoto J, Hoshikawa M, Einama T, Noro T, Aosasa S, et al. Stapler sizes optimized for pancreatic thickness can reduce pancreatic fistula incidence after distal pancreatectomy. Surg Today. 2019;50:623–31. https://doi.org/10.1007/s00595-019-01929-z.
10. Dokmak S, Fteriche FS, Meniconi RL, Aussilhou B, Duquesne I, Perrone G, et al. Pancreatic fistula following laparoscopic distal pancreatectomy is probably unrelated to the stapler size but to the drainage modality and significantly decreased with a small suction drain. Langenbecks Arch Surg. 2019;404(2):203–12. https://doi.org/10.1007/s00423-019-01756-3.
11. Kawaida H, Kono H, Amemiya H, Hosomura N, Saito R, Takahashi K, et al. Use of a reinforced triple-row stapler following distal pancreatectomy reduces the incidence of postoperative pancreatic fistula in patients with a high BMI. Anticancer Res. 2019;39(2):1013–8. https://doi.org/10.21873/anticanres.13207.
12. Sahay SJ, Lykoudis PM, Al Midani A, Haswell A, Rahman SH. Vascular stapler for transection of pancreatic parenchyma in laparoscopic distal Pancreatectomy. Am Surg. 2019;85(6):e275–e6.
13. Kondo N, Uemura K, Nakagawa N, Okada K, Kuroda S, Sudo T, et al. A multicenter, randomized, controlled trial comparing reinforced staplers with bare staplers during distal Pancreatectomy (HiSCO-07 trial). Ann Surg Oncol. 2019;26(5):1519–27. https://doi.org/10.1245/s10434-019-07222-0.
14. Zhang H, Zhu F, Shen M, Tian R, Shi CJ, Wang X, et al. Systematic review and meta-analysis comparing three techniques for pancreatic remnant closure following distal pancreatectomy. Br J Surg. 2015;102(1):4–15. https://doi.org/10.1002/bjs.9653.
15. Søreide K, Healey AJ, Mole DJ, Parks RW. Pre-, peri- and post-operative factors for the development of pancreatic fistula after pancreatic surgery. HPB (Oxford). 2019;21(12):1621–31. https://doi.org/10.1016/j.hpb.2019.06.004.
16. Miao Y, Lu Z, Yeo CJ, Vollmer CM Jr, Fernandez-Del Castillo C, Ghaneh P, et al. Management of the pancreatic transection plane after left (distal) pancreatectomy: expert consensus guidelines by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2020;168:72–84. https://doi.org/10.1016/j.surg.2020.02.018.
17. Sugimoto M, Kendrick ML, Farnell MB, Nomura S, Takahashi N, Kobayashi T, et al. Relationship between pancreatic thickness and staple height is relevant to the occurrence of pancreatic fistula after distal pancreatectomy. HPB (Oxford). 2019;22:398–404. https://doi.org/10.1016/j.hpb.2019.07.010.
18. Seykora TF, Liu JB, Maggino L, Pitt HA, Vollmer CM Jr. Drain management following distal pancreatectomy: characterization of contemporary practice and impact of early removal. Ann Surg. 2019. Publish Ahead of Print. https://doi.org/10.1097/sla.0000000000003205.
19. Machado MCC, Machado MAC. Drainage after distal pancreatectomy: still an unsolved problem. Surg Oncol. 2019;30:76–80. https://doi.org/10.1016/j.suronc.2019.06.002.
20. Andersson R, Søreide K, Ansari D. The dilemma of drains after pancreatoduodenectomy: still an issue? Scand J Surg. 2019;1457496919866014:145749691986601. https://doi.org/10.1177/1457496919866014.
21. Strickland M, Hallet J, Abramowitz D, Liang S, Law CH, Jayaraman S. Lateral approach in laparoscopic distal pancreatectomy is safe and potentially beneficial compared to the traditional medial approach. Surg Endosc. 2015;29(9):2825–31. https://doi.org/10.1007/s00464-014-3997-5.
22. Soreide K, Nymo LS, Kleive D, Olsen F, Lassen K. Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system. Pancreatology. 2019;19(6):880–7. https://doi.org/10.1016/j.pan.2019.07.047.

23. Collard M, Marchese T, Guedj N, Cauchy F, Chassaing C, Ronot M, et al. Is routine Splenectomy justified for all left-sided pancreatic cancers? Histological reappraisal of splenic Hilar lymphadenectomy. Ann Surg Oncol. 2019;26(4):1071–8. https://doi.org/10.1245/s10434-018-07123-8.
24. Milito P, Aiolfi A, Asti E, Rausa E, Bonitta G, Bonavina L. Impact of spleen preserving laparoscopic distal Pancreatectomy on postoperative infectious complications: systematic review and meta-analysis. J Laparoendosc Adv Surg Tech A. 2019;29(2):167–77. https://doi.org/10.1089/lap.2018.0738.
25. Paiella S, De Pastena M, Korrel M, Pan TL, Butturini G, Nessi C, et al. Long term outcome after minimally invasive and open Warshaw and Kimura techniques for spleen-preserving distal pancreatectomy: international multicenter retrospective study. Eur J Surg Oncol. 2019;45(9):1668–73. https://doi.org/10.1016/j.ejso.2019.04.004.
26. Moekotte AL, Lof S, White SA, Marudanayagam R, Al-Sarireh B, Rahman S, et al. Splenic preservation versus splenectomy in laparoscopic distal pancreatectomy: a propensity score-matched study. Surg Endosc. 2019;34:1301–9. https://doi.org/10.1007/s00464-019-06901-z.
27. Dai MH, Shi N, Xing C, Liao Q, Zhang TP, Chen G, et al. Splenic preservation in laparoscopic distal pancreatectomy. Br J Surg. 2017;104(4):452–62. https://doi.org/10.1002/bjs.10434.
28. Liao TK, Wang CJ, Su PJ, Lui WH, Chao YJ, Sy ED et al. Laparoscopic splenic vessels and spleen preservation distal pancreatectomy via inferior-posterior splenic vein approach. Surg Laparosc Endosc Percutan Tech. 2020. Publish Ahead of Print. https://doi.org/10.1097/sle.0000000000000804.
29. Kimura W, Inoue T, Futakawa N, Shinkai H, Han I, Muto T. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. Surgery. 1996;120(5):885–90. https://doi.org/10.1016/s0039-6060(96)80099-7.
30. Warshaw AL. Conservation of the spleen with distal pancreatectomy. Arch Surg. 1988;123(5):550–3. https://doi.org/10.1001/archsurg.1988.01400290032004.
31. Hu YH, Qin YF, Yu DD, Li X, Zhao YM, Kong DJ, et al. Meta-analysis of short-term outcomes comparing robot-assisted and laparoscopic distal pancreatectomy. J Comp Eff Res. 2020;9:201–18. https://doi.org/10.2217/cer-2019-0124.
32. Antila A, Ahola R, Sand J, Laukkarinen J. Management of postoperative complications may favour the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012-2014. Pancreatology. 2019;19(1):26–30. https://doi.org/10.1016/j.pan.2018.11.012.
33. Maatman TK, Butler JR, Quigley SN, Loncharich AJ, Crafts T, Ceppa EP, et al. Leukocytosis after distal pancreatectomy and splenectomy as a marker of major complication. Am J Surg. 2019;220:354–8. https://doi.org/10.1016/j.amjsurg.2019.12.004.
34. Eguia E, Kuo PC, Sweigert P, Nelson M, Aranha GV, Abood G, et al. The laparoscopic approach to distal pancreatectomy is a value-added proposition for patients undergoing care in moderate-volume and high-volume centers. Surgery. 2019;166(2):166–71. https://doi.org/10.1016/j.surg.2019.04.019.
35. Daniel FE, Tamim HM, Hosni MN, Mailhac AC, Khalife MJ, Jamali FR et al. Short-term surgical morbidity and mortality of distal pancreatectomy performed for benign versus malignant diseases: a NSQIP analysis. Surg Endosc. 2019. https://doi.org/10.1007/s00464-019-07163-5.
36. Soreide K, Olsen F, Nymo LS, Kleive D, Lassen K. A nationwide cohort study of resection rates and short-term outcomes in open and laparoscopic distal pancreatectomy. HPB (Oxford). 2019;21(6):669–78. https://doi.org/10.1016/j.hpb.2018.10.006.
37. de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F, et al. Minimally invasive versus open distal Pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. Ann Surg. 2019;269(1):2–9. https://doi.org/10.1097/sla.0000000000002979.
38. van Hilst J, Strating EA, de Rooij T, Daams F, Festen S, Groot Koerkamp B, et al. Costs and quality of life in a randomized trial comparing minimally invasive and open distal pancreatectomy (LEOPARD trial). Br J Surg. 2019;106(7):910–21. https://doi.org/10.1002/bjs.11147.

39. Lassen K, Nymo LS, Olsen F, Søreide K. Benchmarking of aggregated length of stay after open and laparoscopic surgery for cancers of the digestive system. BJS Open. 2018;2(4):246–53. https://doi.org/10.1002/bjs5.67.
40. Lof S, Moekotte AL, Al-Sarireh B, Ammori B, Aroori S, Durkin D, et al. Multicentre observational cohort study of implementation and outcomes of laparoscopic distal pancreatectomy. Br J Surg. 2019;106(12):1657–65. https://doi.org/10.1002/bjs.11292.
41. Rosales-Velderrain A, Bowers SP, Goldberg RF, Clarke TM, Buchanan MA, Stauffer JA, et al. National trends in resection of the distal pancreas. World J Gastroenterol. 2012;18(32):4342–9. https://doi.org/10.3748/wjg.v18.i32.4342.
42. Vining CC, Hogg ME. How to train and evaluate minimally invasive pancreas surgery. J Surg Oncol. 2020;122:41–8. https://doi.org/10.1002/jso.25912.
43. Hogg ME, Besselink MG, Clavien PA, Fingerhut A, Jeyarajah DR, Kooby DA, et al. Training in minimally invasive pancreatic resections: a paradigm shift away from "see one, do one, teach one". HPB (Oxford). 2017;19(3):234–45. https://doi.org/10.1016/j.hpb.2017.01.016.
44. Asbun HJ, Moekotte AL, Vissers FL, Kunzler F, Cipriani F, Alseidi A, et al. The Miami international evidence-based guidelines on minimally invasive pancreas resection. Ann Surg. 2020;271(1):1–14. https://doi.org/10.1097/sla.0000000000003590.
45. Moekotte AL, Rawashdeh A, Asbun HJ, Coimbra FJ, Edil BH, Jarufe N, et al. Safe implementation of minimally invasive pancreas resection: a systematic review. HPB (Oxford). 2019;22:637–48. https://doi.org/10.1016/j.hpb.2019.11.005.
46. Roussel E, Clement G, Lenne X, Pruvot FR, Schwarz L, Theis D, et al. Is centralization needed for patients undergoing distal pancreatectomy?: a nationwide study of 3314 patients. Pancreas. 2019;48(9):1188–94. https://doi.org/10.1097/mpa.0000000000001410.
47. Ohtsuka T, Ban D, Nakamura Y, Nagakawa Y, Tanabe M, Gotoh Y, et al. Difficulty scoring system in laparoscopic distal pancreatectomy. J Hepatobiliary Pancreat Sci. 2018;25(11):489–97. https://doi.org/10.1002/jhbp.578.
48. Partelli S, Ricci C, Rancoita PMV, Montorsi R, Andreasi V, Ingaldi C et al. Preoperative predictive factors of laparoscopic distal pancreatectomy difficulty. HPB (Oxford). 2020. https://doi.org/10.1016/j.hpb.2020.04.002.
49. Goh BKP, Kabir T, Koh YX, Teo JY, Lee SY, Kam JH, et al. External validation of the Japanese difficulty scoring system for minimally-invasive distal pancreatectomies. Am J Surg. 2019;218(5):967–71. https://doi.org/10.1016/j.amjsurg.2019.03.012.
50. Roalsø M, Aunan JR, Søreide K. Refined TNM-staging for pancreatic adenocarcinoma—real progress or much ado about nothing? Eur J Surg Oncol. 2020. https://doi.org/10.1016/j.ejso.2020.02.014.
51. Hank T, Hinz U, Tarantino I, Kaiser J, Niesen W, Bergmann F, et al. Validation of at least 1 mm as cut-off for resection margins for pancreatic adenocarcinoma of the body and tail. Br J Surg. 2018;105(9):1171–81. https://doi.org/10.1002/bjs.10842.
52. Paye F, Micelli Lupinacci R, Bachellier P, Boher JM, Delpero JR. Distal pancreatectomy for pancreatic carcinoma in the era of multimodal treatment. Br J Surg. 2015;102(3):229–36. https://doi.org/10.1002/bjs.9708.
53. Nelson DW, Chang SC, Grunkemeier G, Dehal AN, Lee DY, Fischer TD, et al. Resectable distal pancreas cancer: time to reconsider the role of upfront surgery. Ann Surg Oncol. 2018;25(13):4012–9. https://doi.org/10.1245/s10434-018-6765-2.
54. Lof S, Korrel M, van Hilst J, Alseidi A, Balzano G, Boggi U, et al. Impact of Neoadjuvant therapy in resected pancreatic ductal adenocarcinoma of the pancreatic body or tail on surgical and oncological outcome: a propensity-score matched multicenter study. Ann Surg Oncol. 2019;27:1986–96. https://doi.org/10.1245/s10434-019-08137-6.
55. Gavriilidis P, Roberts KJ, Sutcliffe RP. Laparoscopic versus open distal pancreatectomy for pancreatic adenocarcinoma: a systematic review and meta-analysis. Acta Chir Belg. 2018;118(5):278–86. https://doi.org/10.1080/00015458.2018.1492212.
56. Yang DJ, Xiong JJ, Lu HM, Wei Y, Zhang L, Lu S, et al. The oncological safety in minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma: a

systematic review and meta-analysis. Sci Rep. 2019;9(1):1159. https://doi.org/10.1038/s41598-018-37617-0.
57. van Hilst J, Korrel M, de Rooij T, Lof S, Busch OR, Groot Koerkamp B, et al. Oncologic outcomes of minimally invasive versus open distal pancreatectomy for pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. Eur J Surg Oncol. 2019;45(5):719–27. https://doi.org/10.1016/j.ejso.2018.12.003.
58. Kim EY, Hong TH. Initial experience with laparoscopic radical antegrade modular pancreatosplenectomy for left-sided pancreatic cancer in a single institution: technical aspects and oncological outcomes. BMC Surg. 2017;17(1):2. https://doi.org/10.1186/s12893-016-0200-z.
59. Yoon YS, Han HS, Cho JY, Choi Y, Choi J. Laparoscopic radical antegrade modular pancreatosplenectomy. J Visc Surg. 2016;2:122. https://doi.org/10.21037/jovs.2016.07.07.
60. Choi SH, Kang CM, Lee WJ, Chi HS. Multimedia article. Laparoscopic modified anterior RAMPS in well-selected left-sided pancreatic cancer: technical feasibility and interim results. Surg Endosc. 2011;25(7):2360–1. https://doi.org/10.1007/s00464-010-1556-2.
61. Lee SH, Kang CM, Hwang HK, Choi SH, Lee WJ, Chi HS. Minimally invasive RAMPS in well-selected left-sided pancreatic cancer within Yonsei criteria: long-term (>median 3 years) oncologic outcomes. Surg Endosc. 2014;28(10):2848–55. https://doi.org/10.1007/s00464-014-3537-3.
62. Ome Y, Hashida K, Yokota M, Nagahisa Y, Michio O, Kawamoto K. Laparoscopic radical antegrade modular pancreatosplenectomy for left-sided pancreatic cancer using the ligament of Treitz approach. Surg Endosc. 2017;31(11):4836–7. https://doi.org/10.1007/s00464-017-5561-6.
63. Kim S, Yoon YS, Han HS, Cho JY. Laparoscopic subtotal pancreatectomy with radical antegrade modular pancreatosplenectomy for left-sided pancreatic cancer. Surg Oncol. 2019;28:150. https://doi.org/10.1016/j.suronc.2018.12.006.
64. Zhang G, Kang Y, Zhang H, Wang F, Liu R. Robotic radical antegrade modular pancreatosplenectomy (RAMPS) versus standard retrograde pancreatosplenectomy (SRPS): study protocol for a randomized controlled trial. Trials. 2020;21(1):306. https://doi.org/10.1186/s13063-020-04250-0.
65. De Pastena M, Esposito A, Paiella S, Surci N, Montagnini G, Marchegiani G et al. Cost-effectiveness and quality of life analysis of laparoscopic and robotic distal pancreatectomy: a propensity score-matched study. Surg Endosc. 2020. https://doi.org/10.1007/s00464-020-07528-1.
66. Xourafas D, Cloyd JM, Clancy TE, Pawlik TM, Ashley SW. Identifying hospital cost savings opportunities by optimizing surgical approach for distal pancreatectomy. J Gastrointest Surg. 2019;23(6):1172–9. https://doi.org/10.1007/s11605-018-4002-8.
67. Magge DR, Zenati MS, Hamad A, Rieser C, Zureikat AH, Zeh HJ, et al. Comprehensive comparative analysis of cost-effectiveness and perioperative outcomes between open, laparoscopic, and robotic distal pancreatectomy. HPB (Oxford). 2018;20(12):1172–80. https://doi.org/10.1016/j.hpb.2018.05.014.
68. Fisher AV, Fernandes-Taylor S, Schumacher JR, Havlena JA, Wang X, Lawson EH, et al. Analysis of 90-day cost for open versus minimally invasive distal pancreatectomy. HPB (Oxford). 2019;21(1):60–6. https://doi.org/10.1016/j.hpb.2018.07.003.
69. Conlon KC, de Rooij T, van Hilst J, Abu Hidal M, Fleshman J, Talamonti M, et al. Minimally invasive pancreatic resections: cost and value perspectives. HPB (Oxford). 2017;19(3):225–33. https://doi.org/10.1016/j.hpb.2017.01.019.

Chapter 64
Distal Pancreatectomy with Celiac Artery Resection (DP-CAR)

Sjors Klompmaker, Olivier R. Busch, Herbert J. Zeh, and Marc G. Besselink

Take Home Messages

- This chapter describes a standardized approach to distal pancreatectomy with celiac axis resection (DP-CAR) based on expert consensus and international evidence.
- DP-CAR is a safe and effective operation when performed at specialized high-volume centers on carefully selected patients who received neoadjuvant chemotherapy.
- In those cases, mortality rates are acceptable and median overall survival times can exceed 30 months. However, the aggregated median overall survival time based on 22 published reports (N = 524) is 21 months.
- Treatment of older patients with serious co-morbidities, lack of neoadjuvant chemotherapy, extensive vascular resections, and/or lack of procedure-specific surgical experience may lead to detrimental outcomes including a higher risk of 90-day mortality.

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Pearls and Pitfalls

- + DP-CAR expands surgical eligibility for selected patients with locally advanced pancreatic cancer involving the celiac axis.
- + Eligibility and survival for DP-CAR have increased over the past decade as a result of down staging with more effective neoadjuvant therapy regimens, such as FOLFIRINOX chemotherapy.
- − DP-CAR is associated with higher major morbidity (33%) and 90-day mortality (6%) than conventional pancreatectomy, although these rates are lower at high-volume centers in combination with careful patient selection.
- − Severe ischemic (i.e. gastric or hepatic) complications may occur as a result of the extensive vascular resection. Theoretically, these risks might be reduced by preoperative common hepatic artery embolization, gastric artery preservation, or bypass grafting, but the evidence on these strategies is weak.

Future Perspectives

- Future research should aim to improve insights in pancreatic cancer pathophysiology, improve post-resection collateral flow to the liver and stomach, and reduce severe pancreatectomy-related complications.
- Individualized chemotherapy regimen, immune therapy, or genetic/epigenetic approaches may effectively target the systemic component of pancreatic cancer in the future.
- Improved understanding of anatomical variations and the physiology of collateral flow could improve resection and reconstruction techniques and reduce ischemic complications.
- New strategies to prevent postoperative pancreatic fistula may prevent post-pancreatectomy hemorrhage, abscesses, or other serious postoperative complications.

64.1 Introduction

Pancreas surgeons have traditionally differentiated between resectable, borderline resectable and locally-advanced pancreatic cancer [1]. While local and locally-advanced pancreatic cancer are two distinct stages of the disease, definitions for surgical resectability are continuously debated and updated. In part, this is the result of improved treatment modalities like neoadjuvant chemotherapy, which result in higher **surgical eligibility** rates. On the other hand, new evidence or new surgical tools also shift the boundaries of resectability. Although resectability itself is a relative concept, influenced by locoregional practice variations, radical surgical removal of the primary tumor is key to acceptable overall survival [2]. Currently, only 20–30% of patients with pancreatic cancer undergo resection. If surgical eligibility rates can be expanded, more patients may benefit from radical surgical resection [2].

Recent international studies show that a subgroup of patients with pancreatic cancer, localized in the pancreatic tail or tail and extending into the celiac axis, may benefit from distal pancreatectomy with celiac axis resection (DP-CAR). This

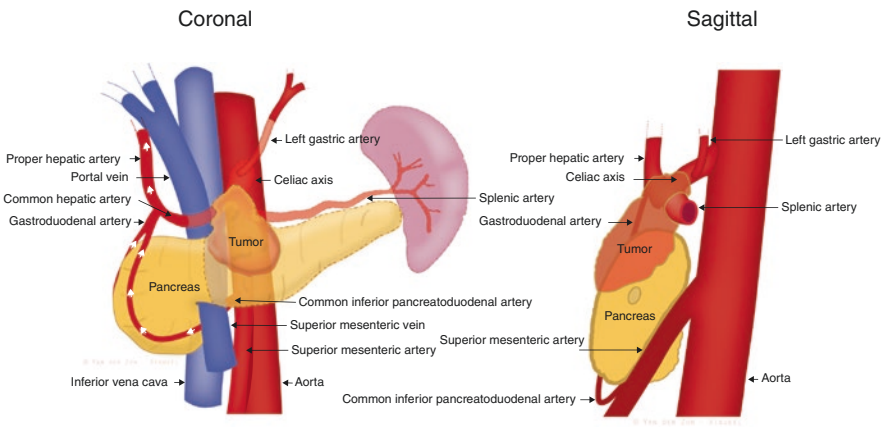

Fig. 64.1 Schematic overview of the anatomy related to DP-CAR. The transparent organs are resected during DP-CAR. The arrows represent reversed flow after resection. The actual anatomical lay-out may differ from this schematic representation. (Drawing by Van der Zon Visueel)

procedure was previously referred to as the modified Appleby procedure [3–5]. After resection of the celiac axis, the liver is perfused by retrograde flow from the superior mesenteric artery via the pancreatic head arcade into the gastroduodenal artery. If the left gastric artery is also resected, the stomach is perfused via the right gastric artery (Fig. 64.1). For this operation, the aorta, gastroduodenal and superior mesenteric arteries should be free of tumor. Additionally, the patient should be fit enough to undergo such extensive surgery. When performed at specialized and high-volume pancreatic surgery centers, after induction or neoadjuvant chemotherapy (FOLFIRINOX [FOLic acid, Fluorouracil, IRINotecan, OXaliplatin] or Nab-Gem-S1 [Nab-Paclitaxel, Gemcitabine, Tegafur/Gimeracil/Oteracil]), complication rates are acceptable and median postoperative overall survival can reach up to 30 months [5, 6].

Here, we describe the standardized approach to DP-CAR with and without left gastric artery preservation. We discuss the role of preoperative artery embolization and a clinical risk score to determine which patients may benefit from DP-CAR. We also touch on additional venous or arterial resection and reconstruction, without going into detail on these experimental procedures. Finally, we present an updated evidence table of a previously published systematic review on DP-CAR.

64.2 Patient Selection and Preoperative Work-Up

From previous studies we know that patient selection is critical to achieve acceptable outcomes after DP-CAR [5, 6]. Each patient should be discussed within a multidisciplinary team and should meet at least the following criteria at baseline: (1) recent CT-/MRI-imaging is available, (2) there are no distant metastases on imaging, (3) the tumor is confined to the pancreatic body/head and the celiac axis,

leaving the aorta, superior mesenteric artery and the gastroduodenal artery free of tumor, (4) the patient completes at least 2–4 months of preoperative chemotherapy. Other relative selection criteria are (5) no concurrent organ involvement, (6) adequate physical condition to undergo maximally invasive surgery, and (7) availability of a surgical team performing at least one DP-CAR per year. The impact of the last three criteria on the risk of 90-day mortality can be assessed using a validated risk calculator (www.panreascalculator.com) [6].

Comparison of results between high- and low-volume centers has taught us that preoperative chemotherapy using FOLFIRINOX or Gemcitabine/nab-paclitaxel/S-1 may greatly improve survival after resection. This effect is attributed partly to self-selection of patients with less aggressive tumors (i.e. less likely to metastasize) that remain stable or partially respond after neoadjuvant treatment and partly to the effective combination of systemic and local therapy [6]. The latter may also be enhanced by preoperative stereotactic body radiation therapy (SBRT) [7]. After preoperative treatment, tumor response should be evaluated using the response evaluation criteria in solid tumors (RECIST) and the change in CA 19.9 levels [8].

Although strong evidence on its efficacy is lacking, some centers apply preoperative artery embolization (PAE) to evaluate and enhance collateral flow to the liver and/or stomach [9]. Additionally, PAE may reduce the risk of postoperative ischemic complications [4, 6, 9–11]. The treatment is based on coiling of the common hepatic artery and/or the left gastric arteries 2–3 weeks prior to surgery. If the aim is to preserve the left gastric artery, only the common hepatic artery should be coiled. After coiling, the collateral flow can be tested on CT-angiography or conventional angiography. In case of insufficient collateral flow, the coils can be removed and the procedure can either be aborted or arterial bypass surgery can be considered. Recommended steps for preoperative selection and workup, including preoperative chemo−/radiotherapy and embolization, are outlined in Fig. 64.2.

64.3 Technical Aspects

64.3.1 Conventional Resection

The patient is placed in supine position and **staging laparoscopy** is performed to rule out peritoneal or liver metastases. Hereafter, a bilateral subcostal or midline laparotomy is performed followed by a second inspection of the liver, peritoneum, and lesser sac. Optionally, intra-operative ultrasonography is performed to confirm tumor involvement of the celiac axis, and rule out involvement of the aorta, superior mesenteric and gastroduodenal arteries and portal vein. At this stage, preoperative CT-/MRI-imaging or visual inspection alone are deemed unreliable as a result of residual inflammation after neoadjuvant chemotherapy. Intraoperative **frozen sections** are taken liberally throughout the operation to confirm the ultrasound findings and the possibility to achieve radical (R0) resection.

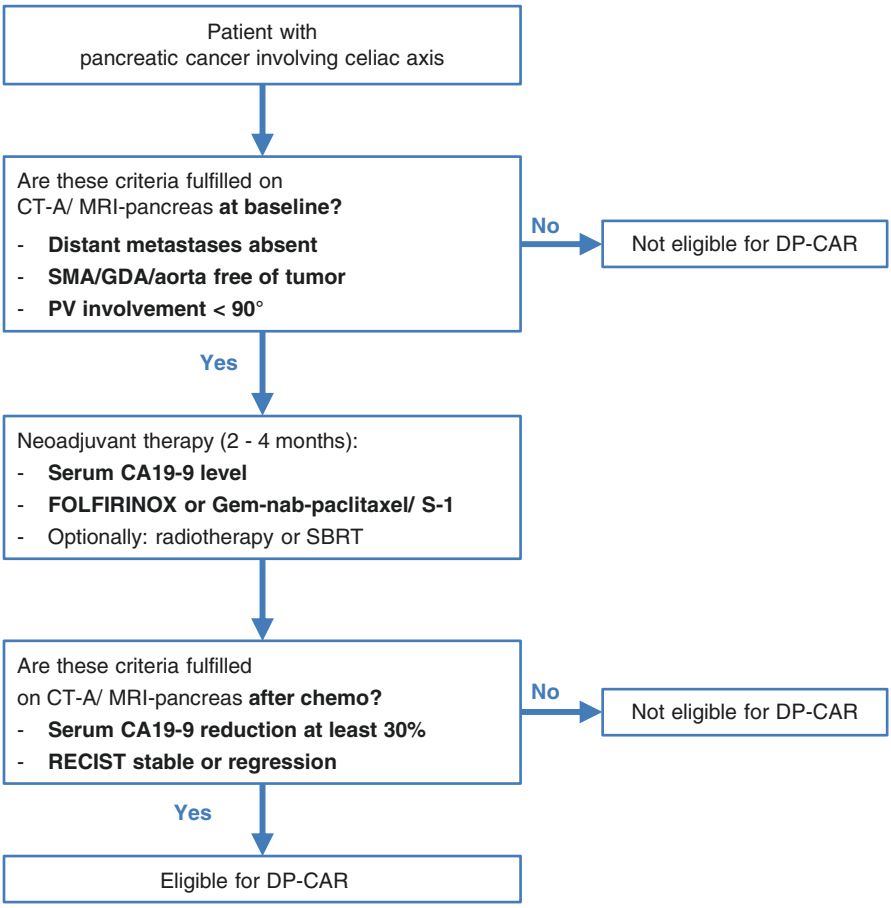

Fig. 64.2 Recommended steps for patient selection and preoperative work up. Consensus recommendations based on multicenter evidence and expert opinions. *CT-A* computed tomography angiogram, *GDA* gastroduodenal artery, *Gem* gemcitabine, *MRI* magnetic resonance imaging, *SBRT* stereotactic body radiation therapy, *PV* portal vein, *RECIST* Response Evaluation Criteria in solid tumors. (Reprinted with permission from: Klompmaker et al. Journal of Gastrointestinal Surgery; 2018)

The operation proceeds with dissection of Treitz' ligament to again assess tumor involvement of the superior mesenteric artery. The inferior vena cava, aorta, and origin of the celiac axis and superior mesenteric artery are exposed using an extended Kocher maneuver. The celiac axis and superior mesenteric artery are encircled with vessel loops if technically feasible. Tumor involvement of the celiac axis and superior mesenteric artery is now confirmed once more. The pancreas is encircled with vessel loops at its neck, ventral to the portomesenteric vein. Lymph node dissection is performed along the hepatic artery (station 8a) as part of routine lymphadenectomy.

The hepatic artery is inspected and **test-occluded** using a bulldog clamp. Adequate collateral flow to the liver via the proper hepatic artery should now be established using a Doppler probe. This step is omitted if the hepatic artery was embolized preoperatively. The diaphragmatic crus is divided cranially to the celiac axis to create space for resection. Celiac axis involvement is once more confirmed by frozen section. Using vascular staplers, the hepatic artery is transected at 1 cm proximal to the gastroduodenal artery and at the base of the celiac axis. Suture and clip closure can be applied when there is not enough space for the stapler. Of note, the left gastric artery may be spared if it shows no tumor involvement and if its origin lays very proximal to the aorta [12].

After a frozen section of the pancreas, the pancreas is now divided in between the vessel loops ventral to the porto-mesenteric vein using a stapler, surgical blade or cautery device. The left gastric vein and the splenic artery and vein are divided. It is important to **preserve the right gastric and gastroepiploic arteries** to reduce the risk of gastric ischemia. The dissection continues dorsally to free the superior mesenteric artery of all nervous and lymphatic tissue on its left side.

The operation now follows the steps of a regular radical antegrade modular pancreato-splenectomy (RAMPS) [13]. Using the **left renal vein** as a landmark, medial to lateral dissection includes the anterior renal fascia (Gerota), pancreatic tail, short gastric vessels, and spleen. An anterior RAMPS (i.e. including the anterior renal fascia) or posterior RAMPS (i.e. including the left adrenal gland) is advised according to the extent of dorsal tumor ingrowth to achieve a radical resection. Lymphadenectomy should include stations 11 (supra-pancreatic) and 18 (infra-pancreatic), according to international study group on pancreatic surgery (ISGPS) recommendations [14]. Lymph station 10 is included in the splenectomy.

Optionally, a wedge or segmental portal vein resection may be carried out as final step, provided involvement is detected perioperatively and adequate exposure can be achieved. A peritoneal patch may be used if only the left lateral aspect of the porto-mesenteric confluence is involved [15]. Otherwise, a segmental resection is performed followed by autologous or synthetic graft insertion. Notably, the pancreatic head remnant likely prevents tension-free endo-to-end anastomosis. This is one of the reasons **vascular reconstructions are riskier** in DP-CAR compared to pancreatoduodenectomy.

Finally, the pancreatic tail and spleen are removed en-bloc, together with the celiac axis. The abdomen is closed after adequate hepatic artery flow is confirmed by visual inspection and Doppler probing. A surgical drain is left in situ at the pancreatic cut margin, with extra side holes at the upper left quadrant. An overview of all recommended steps is presented in Fig. 64.3.

64.3.2 Robot Assisted Approach

Although rarely performed, the robot-assisted DP-CAR may reduce morbidity and mortality rates compared to open in the hands of experienced robotic pancreas surgeons at high-volume centers [6, 16]. Similar to the open approach, the operation is

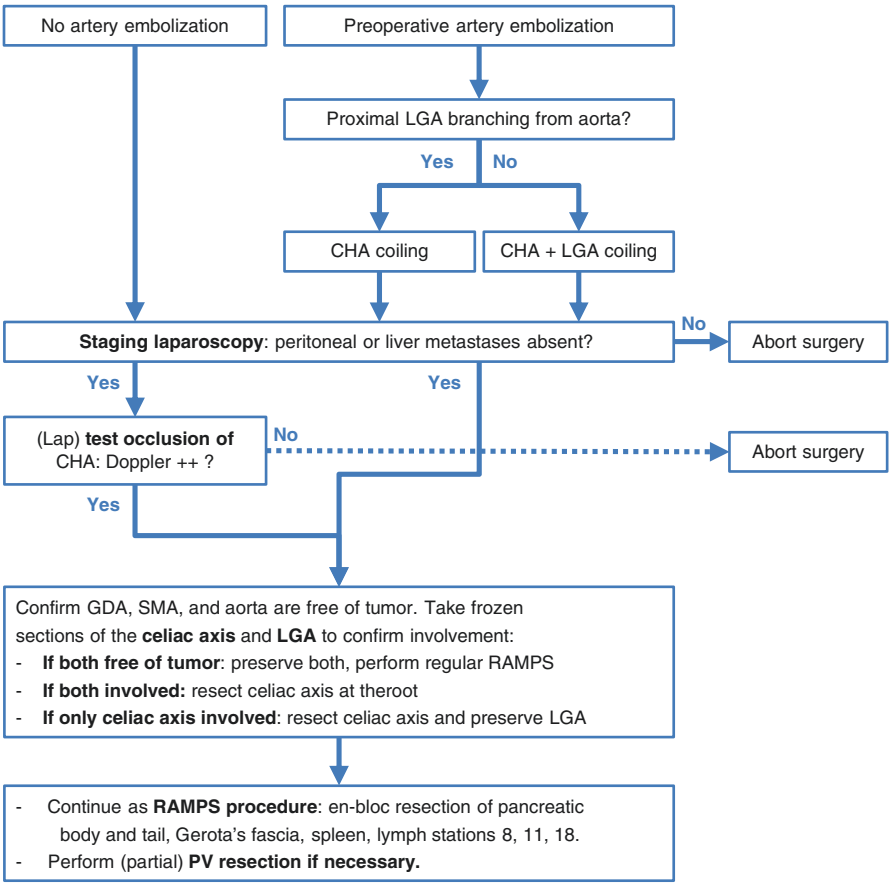

Fig. 64.3 Procedural steps of the DP-CAR. Consensus recommendations based on multicenter evidence and expert opinions. *CHA* common hepatic artery, *GDA* gastroduodenal artery, *lap* laparoscopic, *LGA* left gastric artery, *PV* portal vein, *RAMPS* radical antegrade modular pancreatosplenectomy, *SMV* superior mesenteric vein. (Reprinted with permission from: Klompmaker et al. Journal of Gastrointestinal Surgery; 2018)

preceded by **staging laparoscopy**. Hereafter, the robot is docked and set up next to two laparoscopic trocars, as described elsewhere [16]. The omental bursa is opened and the pancreas is tunneled and encircled with vessel loops. Similar to the open approach, test clamping is performed to check the collateral flow prior to resection. A robotic or laparoscopic non-reinforced linear stapler is then used to divide the pancreas followed by the common hepatic artery. The superior mesenteric artery is then located through further dissection and traced back to its origin at the celiac axis. A robotic ultrasound device is used frequently to confirm the origins of the superior mesenteric artery and the celiac axis.

Using a vascular linear stapler, the splenic artery and left gastric artery and vein are transected distally to their origin at the celiac axis. This is followed by lymphadenectomy on the superior and right side of the celiac axis. Then, the dissection

continues along the adrenal vein from lateral to medial, lifting the distal pancreas and spleen including the renal fascia off of the retroperitoneum. Ligation of the splenic artery and vein, and distal pancreas at the hilum of the spleen and "in situ splenectomy" is performed in most cases to facilitate manipulation of the distal pancreas during dissection of the retroperitoneum. These steps ensure the surgeon has **270-degree access** to the celiac trunk at its origin from the aorta. Thus, the dissection to isolate and divide the celiac axis can proceed in any of these planes. Providing the portal vein shows no tumor involvement at this stage, the splenic vein is divided. Otherwise, splenic vein resection is performed in the final stage. The procedure is concluded by lymphadenectomy on the right side of the celiac axis, followed by transection of the remainder of the celiac axis at its origin using the vascular stapler. All specimens are removed via a pubic (i.e. Pfannenstiel) incision and a surgical drain is left in situ.

64.4 Postoperative Management and International Outcomes

A postoperative enhanced recovery pathway is recommended after DP-CAR, with special attention to clinical or laboratory signs of gastric or hepatic ischemia or infarction [17, 18]. Such signs include abdominal pain or discomfort, delayed gastric emptying, hematemesis from ulceration, or elevated liver enzymes or serum lactate levels. The occurrence of postoperative pancreatic fistula could also indicate ischemia and may cause severe damage to vascular stumps or anastomoses when left untreated. A CT-angiography is indicated at the occurrence of any of the aforementioned symptoms. All patients should receive proton pump inhibitors for 6 months postoperatively. Otherwise, management and follow-up are similar to oncologic distal pancreatectomy.

An overview of the international literature on outcomes after DP-CAR is presented in Table 64.1. The search strategy and evidence from a previous systematic review published in 2016 were updated in October 2019 [4]. Only cohort studies with 3 subjects or more were included. Overlapping cohorts were removed and case-weighted averages and aggregate proportions were re-established. Compared to the previous systematic review, median age was lower (57 vs. 63 years), PAE was performed less often (26% vs. 36%), neoadjuvant therapy was performed more often (41% vs. 16%), adjuvant therapy was performed more often (62% vs. 51%), and medial overall survival has improved (median 21 vs. 14 months). However, major morbidity (33% vs. 27%), 90-day mortality (6.0% vs. 3.5%), and radical resection rates (68% vs. 75%) were worse compared to the previous systematic review. Higher rates of (neo-)adjuvant therapy and a younger patient population may explain improved survival rates. Suspected underreporting in older studies may have confounded morbidity, mortality and radical resection rates. As shown in a recent international multicenter cohort study, outcomes are considerably better in specialized high-volume pancreatic surgery centers [6].

Table 64.1 Updated international outcomes after DP-CAR

Reference	Country	Inclusion period	N	Sex ratio (M: F)	Median age (y)	PHAE (%)	Radical resection (%)	Major morbidity (%)	Ischemic morbidity (%)	Neo-adjuvant therapy (%)	Adjuvant therapy (%)	90-day mortality (%)	Median survival (m)
Mayumi et al. [19]	Japan	1975–1994	6	4: 2	62	n.r.	n.r.	33	17	n.r.	n.r.	0	9
Sperti et al. [20]	Italy	1989–2007	5	3: 2	70	0	60	80[a]	0	0	60 UN	0	10
Yamamoto et al. [21]	Japan	1991–2009	13	10: 3	64[b]	0	31	92[a]	8	0	31 CT/0 RT	0	21
Konishi et al. [22]	Japan	1992–1998	4	0: 4	57	n.r.	75[c]	33	0	n.r.	n.r.	0	10
Shimura et al. [23]	Japan	1992–2011	14	10: 4	69	n.r.	n.r.	35	21	n.r.	n.r.	0	10
Takahashi et al. [24]	Japan	1993–2010	16	8: 8	65[b]	0	56	56	0	0	n.r.	6[d]	9.7
Hishinuma et al. [25]	Japan	1997–2003	7	4: 3	62	0	57[c]	0	0	0	86 RT/17 CT	0	19
Nakamura et al. [10]	Japan	1998–2015	80	40: 40	65	n.r.	93	17	29	15 CT/2.5 CR	64 CT	2.6[d]	31
Ham et al. [26]	Korea	2000–2014	7	3: 4	58	0	71	n.r.	0	0	29 CT	0	15
Sugiura et al. [27]	Japan	2002–2014	16	10: 6	70	0	62	88	0	0	56 CT	n.r.	18
Gagandeep et al. [28]	USA	2002–2004	3	3: 0	60	33	67	33	0	66 UN	100 RT/100 CT	0	n.r.
Wang et al. [29]	China	2003–2012	15	7: 8	61	0	100	7	0	n.r.	30 CT	7	19
Yoshitomi et al. [30]	Japan	2004–2015	38	26: 12	65	74	63	39	11	82 CR	89	n.r.	39

(continued)

Table 64.1 (continued)

Reference	Country	Inclusion period	N	Sex ratio (M: F)	Median age (y)	PHAE (%)	Radical resection (%)	Major morbidity (%)	Ischemic morbidity (%)	Neo-adjuvant therapy (%)	Adjuvant therapy (%)	90-day mortality (%)	Median survival (m)
Klompmaker et al. [6]	EU/USA/ Japan	2004–2017	191	104: 87	63	32	59	36	30	26 CT/40 CR	59 CT/6.3 CR	9.4	19
Jing et al. [31]	China	2005–2010	24	18: 6	55[b]	n.r.	100[c]	54[a]	25	0	0	n.r.	9.3
Zhou et al. [32]	China	2006–2013	12	8: 4	52	0	n.r.	75[a]	0	n.r.	n.r.	0	10
Denecke et al. [33]	Germany	2007–2009	6	4: 2	63	67	33	33	33	0	83 CT	17	12
Mittal et al. [34]	Australia	2007–2014	7	4: 3	64	0	86	0	0	14 UN	86 UN	0	n.r.
Yoshiya et al. [35]	Japan	2008–2018	20	13:7	68[b]	16	75[c]	40	10	55 CT	70 CT	0	31
Kimura et al. [36]	Japan	2010–2011	3	1: 2	66	0	100[c]	100[a]	n.r.	0	33	0	48
Beane et al. [37]	USA	2011–2012	20	6: 14	64	n.r.	n.r.	15	n.r.	25 UN	n.r.	10	n.r.
Sato et al. [38]	Japan	2011–2014	17	13: 4	68	0	94	41	0	12 CT/5.8 CR	76 CT	0	17
Weighted average of medians or aggregated proportion			**524**	**299: 225**	**55**	**26**[e]	**68**[e]	**33**[e]	**20**[e]	**41**[e]	**62**[e]	**6**[e]	**21**

EU Europe, *RT* radiotherapy, *CR* chemoradiation, *CT* chemotherapy, *UN* unknown adjuvant therapy, *PHAE* preoperative hepatic artery embolization, *n.r.* not reported. Updated table, originally printed in: Klompmaker et al. BJS; 2016

[a]Overall morbidity

[b]Data originally reported as mean (s.d.)

[c]R1/R0 margin definition not reported

[d]30-day mortality

[e]Overall proportions in studies reporting on the outcome

64.5 Conclusion

The standardized DP-CAR is a safe and effective operation when performed at specialized high-volume centers, on carefully selected patients who received neoadjuvant chemotherapy. Based on 22 published reports (N = 524) the 90-day mortality rate was 6% and the median overall survival time was 21 months. However, high-volume centers have reported lower 90-day mortality rates and median overall survival exceeding 30 months.

References

1. Tempero MA, Malafa MP, Chiorean EG, Czito B, Scaife C, Narang AK, et al. Pancreatic adenocarcinoma, version 1.2019 featured updates to the NCCN guidelines. JNCCN J Natl Compr Cancer Netw. 2019;17(3):203–10.
2. Siegel R, Miller K, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
3. Klompmaker S, van Hilst J, Gerritsen SL, Adham M, Teresa Albiol Quer M, Bassi C, et al. Outcomes after distal pancreatectomy with celiac axis resection for pancreatic cancer: a pan-European retrospective cohort study. Ann Surg Oncol. 2018;25(5):1440–7.
4. Klompmaker S, De Rooij T, Korteweg JJ, Van Dieren S, Van Lienden KP, Van Gulik TM, et al. Systematic review of outcomes after distal pancreatectomy with coeliac axis resection for locally advanced pancreatic cancer. BJS. 2016;103(8):941–9.
5. Klompmaker S, Boggi U, Hackert T, Salvia R, Weiss M, Yamaue H, et al. Distal pancreatectomy with celiac Axis resection (DP-CAR) for pancreatic cancer. How I do it. J Gastrointest Surg. 2018;22(10):1804–10.
6. Klompmaker S, Peters NA, van Hilst J, Bassi C, Boggi U, Busch OR, et al. Outcomes and risk score for distal pancreatectomy with celiac axis resection (DP-CAR): an international multicenter analysis. Ann Surg Oncol. 2019;26(3):772–81.
7. Peters NA, Javed AA, Cameron JL, Makary MA, Hirose K, Pawlik TM, et al. Modified Appleby procedure for pancreatic adenocarcinoma: does improved neoadjuvant therapy warrant such an aggressive approach? Ann Surg Oncol. 2016;23(11):3757–64.
8. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1—update and clarification: from the RECIST committee. Eur J Cancer. 2016;62(May):132–7.
9. Kondo S, Katoh H, Shimizu T, Omi M, Hirano S, Ambo Y, et al. Preoperative embolization of the common hepatic artery in preparation for radical pancreatectomy for pancreas body cancer. Hepatogastroenterology. 2000;47(35):1447–9.
10. Nakamura T, Hirano S, Noji T, Asano T, Okamura K, Tsuchikawa T, et al. Distal pancreatectomy with en bloc celiac axis resection (modified Appleby procedure) for locally advanced pancreatic body cancer: a single-center review of 80 consecutive patients. Ann Surg Oncol. 2016;23(Suppl 5):969–75.
11. Cesaretti M, Abdel-Rehim M, Barbier L, Dokmak S, Hammel P, Sauvanet A. Modified Appleby procedure for borderline resectable/locally advanced distal pancreatic adenocarcinoma: a major procedure for selected patients. J Visc Surg. 2016;153(3):173–81.
12. Okada K, Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, et al. Preservation of the left gastric artery on the basis of anatomical features in patients undergoing distal pancreatectomy with celiac Axis En-bloc resection (DP-CAR). World J Surg. 2014;38(11):2980–5.
13. Strasberg SM, Fields R. Left-sided pancreatic cancer. Cancer J. 2012;18(6):562–70.
14. Tol JAMG, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus

statement by the international study group on pancreatic surgery (ISGPS). Surgery. 2014;156(3):591–600.
15. Dokmak S, Aussilhou B, Sauvanet A, Nagarajan G, Farges O, Belghiti J. Parietal peritoneum as an autologous substitute for venous reconstruction in hepatopancreatobiliary surgery. Ann Surg. 2015;262(2):366–71.
16. Ocuin LM, Miller-Ocuin JL, Novak SM, Bartlett DL, Marsh JW, Tsung A, et al. Robotic and open distal pancreatectomy with celiac axis resection for locally advanced pancreatic body tumors: a single institutional assessment of perioperative outcomes and survival. HPB. 2016;18(10):835–42.
17. Coolsen MME, Van Dam RM, Van Der Wilt AA, Slim K, Lassen K, Dejong CHC. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. World J Surg. 2013;37(8):1909–18.
18. Lassen K, Coolsen MME, Slim K, Carli F, de Aguilar-Nascimento JE, Schäfer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: enhanced recovery after surgery (ERAS®) society recommendations. Clin Nutr. 2012;31(6):817–30.
19. Mayumi T, Nimura Y, Kamiya J, Kondo S, Nagino M, Kanai M, et al. Distal pancreatectomy with en bloc resection of the celiac artery for carcinoma of the body and tail of the pancreas. Int J Pancreatol. 1997;22(1):15–21.
20. Sperti C, Berselli M, Pedrazzoli S. Distal pancreatectomy for body-tail pancreatic cancer: is there a role for celiac axis resection? Pancreatology. 2010;10(4):491–8.
21. Yamamoto Y, Sakamoto Y, Ban D, Shimada K, Esaki M, Nara S, et al. Is celiac axis resection justified for T4 pancreatic body cancer? Surgery. 2012;151(1):61–9.
22. Konishi M, Kinoshita T, Nakagori T, Inoue K, Oda T, Kimata T, et al. Distal pancreatectomy with resection of the celiac axis and reconstruction of the hepatic artery for carcinoma of the body and tail of the pancreas. J Hepato Pancreat Surg. 2000;7(2):183–7.
23. Shimura M, Ito M, Horiguchi A, Miyakawa S. Distal pancreatectomy with en bloc celiac axis resection performed while monitoring hepatic arterial flow by using a transonic flowmeter during operation. Hepatogastroenterology. 2012;59(117):1498–500.
24. Takahashi Y, Kaneoka Y, Maeda A, Isogai M. Distal pancreatectomy with celiac axis resection for carcinoma of the body and tail of the pancreas. World J Surg. 2011;35(11):2535–42.
25. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I. Stomach-preserving distal pancreatectomy with combined resection of the celiac artery: radical procedure for locally advanced cancer of the pancreatic body. J Gastrointest Surg. 2007;11(6):743–9.
26. Ham H, Kim SG, Kwon HJ, Ha H, Choi YY. Distal pancreatectomy with celiac axis resection for pancreatic body and tail cancer invading celiac axis. Ann Surg Treat Res. 2015;89(4):167–75.
27. Sugiura T, Okamura Y, Ito T, Yamamoto Y, Uesaka K. Surgical indications of distal pancreatectomy with celiac axis resection for pancreatic body/tail cancer. World J Surg. 2016;41(1):258–66.
28. Gagandeep S, Artinyan A, Jabbour N, Mateo R, Matsuoka L, Sher L, et al. Extended pancreatectomy with resection of the celiac axis: the modified Appleby operation. Am J Surg. 2006;192(3):330–5.
29. Wang X, Dong Y, Jin J, Liu Q, Zhan Q, Chen H, et al. Efficacy of modified Appleby surgery: a benefit for elderly patients? J Surg Res. 2015;194(1):83–90.
30. Yoshitomi H, Sakai N, Kagawa S, Takano S, Ueda A, Kato A, et al. Feasibility and safety of distal pancreatectomy with en bloc celiac axis resection (DP-CAR) combined with neoadjuvant therapy for borderline resectable and unresectable pancreatic body/tail cancer. Langenbecks Arch Surg. 2019;404(4):451–8.
31. Jing W, Zhu G, Hu X, Jing G, Shao C, Zhou Y, et al. Distal pancreatectomy with en bloc celiac axis resection for the treatment of locally advanced pancreatic body and tail cancer. Hepatogastroenterology. 2013;60(121):187–90.
32. Zhou Y-M, Zhang X-F, Li X-D, Liu X-B, Wu L-P, Li B. Distal pancreatectomy with en bloc celiac axis resection for pancreatic body-tail cancer: is it justified? Med Sci Monit. 2014;20:1–5.

33. Denecke T, Andreou A, Podrabsky P, Grieser C, Warnick P, Bahra M, et al. Distal pancreatectomy with en bloc resection of the celiac trunk for extended pancreatic tumor disease: an interdisciplinary approach. Cardiovasc Intervent Radiol. 2011;34(5):1058–64.
34. Mittal A, De Reuver PR, Shanbhag S, Staerkle RF, Neale M, Thoo C, et al. Distal pancreatectomy, splenectomy, and celiac axis resection (DPS-CAR): common hepatic arterial stump pressure should determine the need for arterial reconstruction. Surgery. 2015;157(4):811–7.
35. Yoshiya S, Fukuzawa K, Inokuchi S, Kosai-Fujimoto Y, Sanefuji K, Iwaki K, et al. Efficacy of neoadjuvant chemotherapy in distal pancreatectomy with en bloc celiac axis resection (DP-CAR) for locally advanced pancreatic cancer. J Gastrointest Surg. 2020;24(7):1605–11.
36. Kimura A, Yamamoto J, Aosasa S, Hatsuse K, Nishikawa M, Nishiyama K, et al. Importance of maintaining left gastric arterial flow at Appleby operation preserving whole stomach for central pancreatic cancer. Hepatogastroenterology. 2012;59(120):2650–2.
37. Beane JD, House MG, Pitt SC, Kilbane EM, Hall BL, Parmar AD, et al. Distal pancreatectomy with celiac axis resection: what are the added risks? HPB. 2015;17(9):777–84.
38. Sato T, Inoue Y, Takahashi Y, Mise Y, Ishizawa T, Tanakura K, et al. Distal pancreatectomy with celiac axis resection combined with reconstruction of the left gastric artery. J Gastrointest Surg. 2017;21(5):910–7.

Chapter 65
Evolution of Surgery for Pancreatic Cancer and Future Directions

Oliver Strobel and Markus W. Büchler

Take Home Messages

- Pancreatic cancer surgery has rapidly evolved in the last four decades.
- Mortality has decreased from above 20% to around 3% in high-volume settings.
- Postoperative pancreatic fistula remains a relevant problem both after pancreatoduodenectomy and distal pancreatectomy.
- Surgical resection remains the prerequisite for long-term survival. In combination with modern chemotherapy median survival times above 50 months can be achieved.
- Surgical resection techniques have to aim for local radicality (R0 resection) and should be oriented at the mesenteric and celiac arteries and at the mesenteric and portal veins
- The role of minimally invasive surgery and the best therapy sequencing of resection and chemotherapy are two important topics of current research that will have major impact on the future development of pancreatic cancer surgery.

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Future Perspectives

- Evidence on the effect both of techniques pointed at local radicality and of minimally invasive techniques on short-term (safety) and long-term outcome (efficacy) will be decisive for the future technical development of pancreatic cancer surgery.
- The reduction and management of postoperative pancreatic fistula will remain in the focus of short-term outcomes.
- Evidence from ongoing studies on therapy sequencing (upfront surgery versus neoadjuvant therapy) in resectable and borderline resectable pancreatic cancer will have considerable impact on the role of surgery in the multimodal treatment of pancreatic cancer.
- With advances in both surgical technique and systemic treatment of pancreatic cancer the role of pancreatic cancer surgery is expected to increase in the future.

65.1 Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in the Western world [1] and it is projected to become the second leading cause by 2030 [2]. Surgical resection in combination with systemic chemotherapy offers the only chance of long-term survival and potential cure [3]. However, only about 20–30% of patients with pancreatic cancer present with resectable tumours [3, 4] and even these patients frequently do not undergo potentially curative surgery. Despite the clear survival benefit from resection, several recent population-based studies identified a failure to offer surgery to many patients with stage I-II pancreatic cancer with resection rates varying between 35% and 70% across the USA and Europe [5, 6]. While various mechanisms contribute to this underutilization of surgery, a persisting skepticism of primary care providers and patients towards the safety and efficacy of pancreatic cancer surgery appears to play an important role [3]. Pancreatic resections belong to the most challenging procedures in oncological surgery and are associated with a considerable risk of morbidity and even mortality. In addition, pancreatic cancer remains one of the most deadliest cancers with a high rate of recurrence affecting around 25–40% of patients already in the first year and 5 year survival rates of only around 20 even after successful resection [3]. However, the field of pancreatic cancer surgery has enormously evolved over the last few decades resulting in considerably improved safety and efficacy and continues to rapidly develop.

This chapter gives a brief overview about the evolution of pancreatic cancer surgery and summarizes advances that are of central importance for the optimization of outcomes. Many of these advances were made in areas that do not only involve surgery itself, but the entire management of patients with pancreatic cancer and include preoperative diagnostic workup, perioperative patient care, complication management as well as adjuvant and neoadjuvant therapy.

Advances in these areas are inextricably linked to the past evolution and to the future of pancreatic cancer surgery and are delineated in dedicated chapters within this textbook. This chapter highlights technical aspects in the evolution of

pancreatic cancer surgery. Topics that are currently of main interest and may have considerable impact on the future evolution of pancreatic cancer surgery are highlighted.

65.2 Evolution of Pancreatic Cancer Surgery

The history of pancreatic cancer surgery spans less than 140 years and can be divided in several eras in which the incremental progress was driven by distinct advances in both surgical technique and in other disciplines.

65.2.1 Era of the Pioneers

Even a brief overview on the evolution of pancreatic cancer surgery should pay tribute to the pioneering surgeons, who dared to explore and boldly push forward the frontiers of pancreatic surgery and prepared the ground for modern pancreatic cancer surgery. In the second half of the nineteenth century advances in aseptic techniques and surgical anesthesia were preconditions for the evolution of visceral surgery, when it was in its infancy. Pancreatic surgery started from palliative procedures for the management of biliary obstruction or procedures to manage pseudocysts in pancreatitis [7, 8]. Towards the end of the nineteenth century the first pancreatic resections for malignant tumors were performed (Table 65.1) [9–20].

The first anatomical pancreatic resection for cancer is attributed to Friedrich Trendelenburg, who performed a distal pancreatectomy with splenectomy during a resection for sarcoma in 1882 [9]. Due to the challenges in resection and reconstruction for pancreatic head tumors that we still face today, it took almost three decades until Walther Kausch performed the first successful partial pancreatoduodenectomy for an ampullary cancer as a two-stage procedure in 1909 [13]. The first successful one-stage partial pancreatoduodenectomy was performed by Georg Hirschel in Heidelberg in 1914 [14]. Interestingly, the first combined vascular resection for pancreatic cancer was performed as early as 1927 as a subtotal pancreatectomy with portal vein resection by Gordon Gordon-Taylor in London [15].

While the previous partial pancreatoduodenectomies were non-anatomical, removing only a part of the pancreatic head and duodenum, Allan Whipple performed the first anatomical partial pancreatoduodenectomy as a two-stage procedure for an ampullary cancer in 1934 [16]. The 1935 publication of Whipple and colleagues on pancreatoduodenectomy marks an important event in pancreatic surgery, as it triggered a broader recognition of the procedure and its role in ampullary cancer. However, the first anatomical resection for pancreatic head cancer per se, performed as pylorus-preserving partial pancreatoduodenectomy in 1937, is attributed to Alexander Brunschwig [17]. Although techniques for pancreaticojejunostomy were described as early as 1907 [12], the first partial pancreatoduodenectomies were performed with suture closure for management of the pancreatic remnant, resulting in inevitably high

Table 65.1 Landmarks in the evolution of pancreatic resections for cancer

Year	Surgeon (reference)	Place	Procedure	Appraisal
1882	Friedrich Trendelenburg [9]	Bonn, Germany	Distal pancreatectomy and splenectomy	First anatomical pancreatic resection for a solid tumor (sarcoma)
1898	Alessandro Codivilla [10]	Imola, Italy	One-stage partial PD	First attempted radical PD for cancer (unsuccessful, in hospital death)
1898	William Halsted [11]	Baltimore, USA	Transduodenal excision	First resection for ampullary cancer (performed as local excision)
1907	Abel Desjardins [12]	Paris, France	Pancreaticojejunostomy	First description of anatomical PD and reconstruction with pancreatojejunostomy (based on a study in human cadavers)
1909	Walther Kausch [13]	Berlin, Germany	Two-stage partial PD	First successful (non-anatomical) partial PD (ampullary cancer)
1914	Georg Hirschel [14]	Heidelberg, Germany	One-stage partial PD	First successful one-stage (non-anatomical) partial PD (ampullary cancer)
1927	Gordon Gordon-Taylor [15]	London, England	Subtotal pancreatectomy with portal vein resection	First combined vascular resection for pancreatic cancer.
1934	Allen Whipple [16]	New York, USA	Two-stage PD	First anatomical PD (ampullary cancer)
1937	Alexander Brunschwig [17]	New York, USA	Two-stage PD	First anatomical (pylorus-preserving) PD for pancreatic cancer
1940	Allen Whipple [18]	New York, USA	One-stage anatomic PD	First one-stage anatomical PD
1942	James Priestley [19]	Rochester, USA	Total pancreatectomy	First successful total pancreatectomy (insulinoma)
1994	Gagner and Pomp [20]	Montreal, Canada	Laparoscopic PD	First minimally invasive anatomical pancreatic resection (chronic pancreatitis)

PD partial pancreatoduodenectomy

leakage rates. Pancreatojejunostomy became standard for reconstruction after anatomical partial pancreatoduodenectomy in the early 1940s [7, 18]. The evolution of surgical technique was closely linked to advances in related fields of medicine: The first pancreatoduodenectomies were performed as two-stage procedures with bilioenteric anastomosis to relief cholestasis and improve liver function at stage one followed by tumor resection at stage two. The discovery and clinical implementation of Vitamin K to reverse coagulopathy together with the availability of blood transfusion allowed to establish one-stage procedures as the standard in the 1940s [7].

While these pioneering contributions are important landmarks in the evolution of pancreatic cancer surgery until the 1940s, further progress over the next four decades was inhibited by overall poor outcomes with reported mortality rates ranging between 20 and 40%, and 5-year survival rates after resections for pancreatic cancer

of only 5% [7, 21]. The excessive mortality and poor long-term outcomes hampered broader clinical implementation of pancreatic cancer surgery. Some surgeons even concluded that pancreatoduodenectomy should be abandoned in favor of palliative procedures for the treatment of pancreatic cancer or should even be prohibited by law [22–24].

65.2.2 Era of Standard Clinical Implementation

Standard clinical implementation of oncological resections in the treatment of pancreatic cancer was only achievable by considerable improvements in safety with reduction of the excessive perioperative mortality rates reported until the early 1980s [21]. These essential advances were achieved in a few expert centers for pancreatic surgery led by prominent surgeons around the world. Without the claim of completeness the list of these pancreatic surgeons includes from Europe: Michael Trede of Mannheim, Hans Beger of Ulm, Ingemar Ihse of Lund, David Carter of Edinburgh; from the USA: John Cameron of Baltimore, Andrew Warshaw of Boston, Murray Brennan of New York, Howard Reber of Los Angeles; from Japan: Fujiu Hanyu of Tokyo; and others [21, 25–28]. By establishing tertiary referral centers and, thereby concentrating case volume and experience, these prominent pancreatic surgeons were able to reduce the high mortality rates associated especially with pancreatoduodenectomy to well below 5% and, thereby, to implement pancreatic resection as the standard treatment for resectable pancreatic cancer [26, 27]. Even series of more than 100 consecutive pancreatoduodenectomies without mortality were reported [25]. Volume-outcome effects were recognized to play an important role not only for refinements in surgical techniques of resection and reconstruction, but also for improved perioperative management and for advances in complication management resulting in a reduction of the failure to rescue patients with morbidity [29, 30].

The growing experience and case load of pancreatic cancer surgery in these centers was connected to advances in other disciplines including anesthesia, medical and radiation oncology, diagnostic and interventional radiology, as well as basic and translational pancreatic cancer research. Many of the treatment concepts that define modern pancreatic surgery were initiated in this era. The development of clinical pathways for staging and stage-adjusted treatment [31], the administration of adjuvant therapy after pancreatic cancer resection [32] and the use of neoadjuvant therapy for downstaging of locally advanced cancers [33] are important examples. With the achievement of adequate safety, the efficacy of pancreatic cancer surgery defined by median survival time and 5 year overall survival rates got into the focus. The evolution of pancreatic surgery was further driven by an increased international exchange of knowledge and the formation of study groups that have been instrumental to advance the treatment of pancreatic cancer until today, such as the European Study Group for Pancreatic Cancer (ESPAC) [34].

However, the increased safety reported from high-volume centers also triggered a world-wide trend to perform pancreatic cancer surgery in low-volume settings,

resulting again in poor outcomes. After pancreatic surgery was identified as an area with clear volume-outcome effects [30] a trend for (re-)centralization of pancreatic cancer surgery was triggered in several countries. However, in other countries a significant proportion of pancreatic cancer surgery is still performed in low-volume settings [35].

The prominent pancreatic surgeons named above also trained many of today's leaders of pancreatic surgery. Therefore, their era seamlessly transitions to the present modern era of pancreatic cancer surgery.

65.2.3 Modern Era of Pancreatic Cancer Surgery

The increase in safety has triggered the further evolution of clinical practice and research of pancreatic cancer surgery in several directions that together define today's "modern" era of pancreatic cancer surgery.

With the reduction of perioperative mortality of pancreatic cancer surgery the focus on improving early outcomes has shifted to decreasing the still considerably high morbidity of pancreatic resections and especially the rate of postoperative pancreatic fistula as the most relevant complication. The modern era is characterized by international efforts to establish common definitions for both the most relevant complications and for the extent of resections in order to advance research by enabling standardized reporting in clinical studies. Definitions established by the International Study Group on Pancreatic Surgery (ISGPS) include consensus definitions with severity grading for the complications of postoperative pancreatic fistula, post-pancreatectomy hemorrhage, delayed gastric emptying, and chyle leak [36–40].

These ISGPS definitions have indeed fostered international research and enabled multicenter randomized controlled trials on surgical techniques, such as the division of the pancreas during distal pancreatectomy or the technique of pancreatic anastomosis [41, 42].

In parallel the improved safety of pancreatic cancer surgery led to an expansion of the patient populations undergoing surgery in high-volume settings in several directions:

1. towards offering surgery to older patients with higher comorbidity,
2. towards more advanced tumors requiring multivisceral and vascular resections or resection after downstaging by neodjuvant therapy, but also
3. towards "preemptive" surgery in patients with premalignant tumors such as intraductal papillary mucinous neoplasia (IPMN) [43–48].

Again, this evolution was accompanied by efforts to establish international consensus. The contributions of the ISGPS cover consensus definitions for borderline-resectable pancreatic cancer, extended pancreatectomy, standard lymphadenectomy as well as position statements on the need of preoperative tissue confirmation and techniques of pancreatic anastomoses [49–53].

The optimization of the oncologic outcomes of pancreatic cancer surgery in the modern era is mainly based on progress in two areas, namely the *evolution of surgical techniques* aimed at local radicality, and the *evolution of interdisciplinary and multimodal treatment* algorithms (Fig. 65.1) [3]. Adequate oncologic outcomes in patients with localized pancreatic cancer can only be achieved by the combination

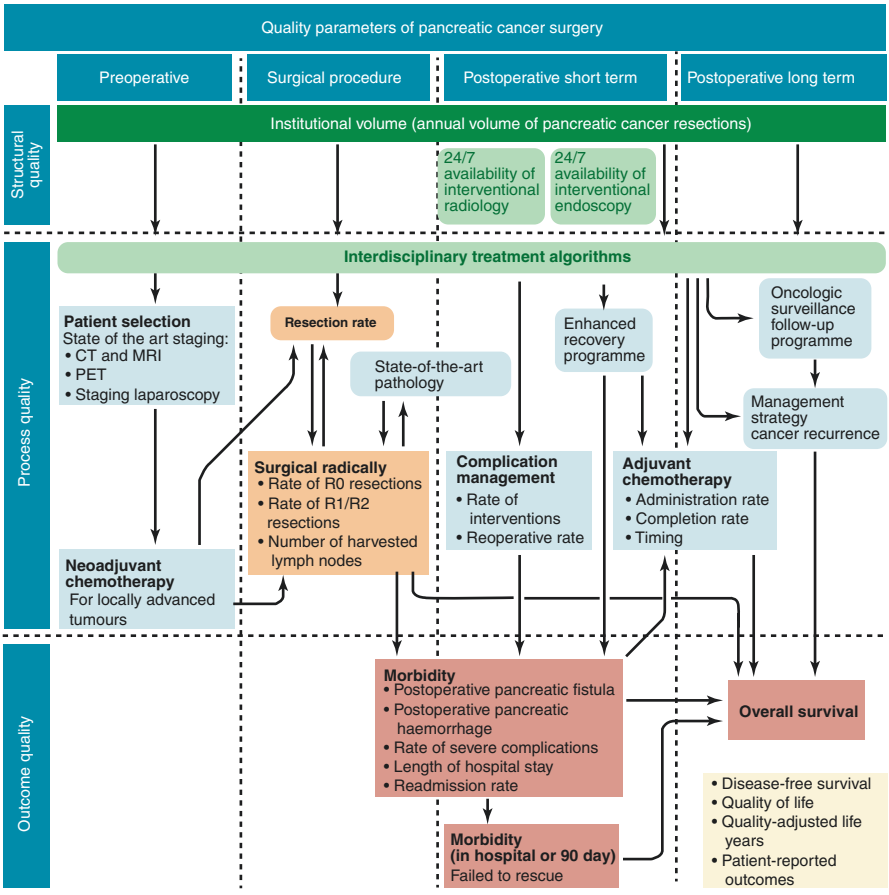

Fig. 65.1 Important quality criteria for pancreatic cancer surgery and their inter-relationships. Different criteria for structural process and outcome quality are relevant at different time points during the treatment pathway. Institutional volume (green) affects all aspects of process and outcome quality. The quality of surgery is essential (orange), although the quality of surgical outcomes is closely dependent on the quality of interdisciplinary treatment involving radiology (in patient resection and complication management), anaesthesia (for patient selection and perioperative care), medical oncology (for patient selection and adjuvant treatment) and others. Overall survival is currently the most important indicator ofoutcome quality. However, in the future, owing to improvements in survival outcomes the importance of disease-free survival and quality of life will increase. (Reproduced with permissions from Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev. Clin Oncol. 2019 Jan;16 (1):11–26)

of radical surgery and systemic chemotherapy administered either in the neoadjuvant or the adjuvant setting [3]. The evolution of adjuvant chemotherapy has been one of the major drivers of modern pancreatic surgery and is topic of another chapter in this textbook. In the following we focus on the evolution of surgical technique.

65.3 Techniques of Modern Pancreatic Cancer Surgery

Techniques of pancreatic cancer surgery have to aim for both safety and efficacy. The main parameters of safety, perioperative (90-day or in-hospital) morbidity and mortality, are essentially determined by the rate of postoperative pancreatic fistula. The efficacy of pancreatic cancer surgery is defined by median survival times and 5-year survival rates as main outcome parameters. In a simplified model the efficacy of pancreatic cancer surgery is mainly determined by local radicality of the resection while its safety is mainly determined by the reconstruction. In reality, safety and efficacy are closely related: Perioperative morbidity, especially postoperative pancreatic fistula and other septic complications have considerable impact on the administration of adjuvant therapy, which in turn is closely associated with survival outcome. Vice versa an increase in local radicality, such as extended lymph node dissections, vascular resections, multivisceral resections, and total pancreatectomy, is associated with an increased risk of morbidity [44, 54, 55]. A final evaluation of any technique in pancreatic cancer surgery, therefore, has to be based on endpoints for both safety and efficacy.

In the following, we focus on techniques relevant for resection, but not for reconstruction. The oncological principles of local radicality of a resection for any gastrointestinal cancer include en-bloc resection of the tumor with clear margins in combination with an adequate extent of lymphadenectomy [56].

Due to the anatomical relationship of the pancreas to major visceral arteries and veins and due to the biology of pancreatic cancer with a predisposition for perineural invasion and growth towards these major vessels, local radicality is more difficult to achieve in pancreatic cancer compared to other gastrointestinal cancers. Radicality of pancreatic cancer resections is pathologically defined by the resection margin (R−) status and determined by the distance of the cancer to the closest margin [57]. The R-status has considerable impact on survival outcome if all relevant margins (including both transection and circumferential margins) are thoroughly evaluated according to current standards [57]. If a pancreatic head cancer was resected with a minimum safety margin of 1 mm, this is associated with a median survival of 42 months and a 38% 5-year survival rate [58]. For left-sided pancreatic cancers the median survival and 5-year survival associated with a 1 mm free margin are even more favorable with 62 months and 53%, respectively [59].

The effect of an extended (retroperitoneal) lymphadenectomy versus a standard (regional perivascular) lymphadenectomy in pancreatic cancer was assessed in several randomized controlled trials. An extended lymphadenectomy does not increase survival but is associated with increased morbidity according to current

evidence and is, therefore, not recommended [54]. The ISGPS has defined a standard lymphadenectomy that includes peripancreatic lymph nodes as well as perivascular lymph nodes along the tumor-oriented side of the superior mesenteric vessels and the celiac axis as well as in the hepatoduodenal ligament [51]. If the techniques listed below are applied these lymph nodes are by default included in the resection.

The following techniques and strategies are aimed at local radicality in pancreatic cancer surgery. Several of these techniques were first described by Japanese surgeons.

65.3.1 Artery First Approaches

Because of perineural invasion of the periarterial plexus most R1 resections for pancreatic cancer are located at the posterior and medial margins oriented towards the superior mesenteric vessels and the celiac axis [57]. With the aims to evaluate resectability early during cancer surgery and to increase local radicality several artery-first approaches have been described [60]. The first such approach (mesenteric approach) was described by Nakao et al. as early as 1993 based on a study in 114 patients [61]. Over time several other artery-first approaches were described and have specific advantages dependent on tumor location in relation to the arteries [60]. Theoretically, artery-first approaches have the following common advantages over the traditional resection technique: (1) Assessment of resectability early during surgical exploration before a point of no return is passed, thus avoiding R2 resections; (2) Increase in radicality at the vessels and in R0 rates; (3) Good control of the vessels resulting in lower blood loss and increased safety. At present the evidence on artery-first approaches is still limited. While a systematic review and meta-analysis of mainly retrospective studies substantiated the presumed advantages for artery-first approaches [62], the first multicenter randomized controlled trial did not [63]. However, the trial protocol only specified the sequence of operative steps, but not the radicality of perivascular resection and it remains unclear if the purpose of a radical dissection was fulfilled. The results of further randomized controlled trials on this important topic are eagerly awaited [64].

65.3.2 Level-III Perivascular Dissection

A pancreatic resection can be performed at different levels around the visceral arteries. In order to achieve the widest possible margin towards the arteries the level of dissection should be directly at the vascular wall, including the removal of the periarterial nerve plexus (Level-III dissection according to Inoue et al.) [65]. One of the technical advantages of artery-first approaches is that they facilitate a level-III dissection.

65.3.3 TRIANGLE-Operation

A radical resection for pancreatic cancer includes a level-III dissection at the tumor-oriented side of the superior mesenteric, celiac and hepatic arteries down to their origin as well as a complete clearance of soft tissue around the superior mesenteric and portal veins (or a venous resection). This will result in an operative site in which the above-named vessels form a triangle free of other tissue (Fig. 65.2). This attribute of a radical resection for pancreatic cancer was first described after neoadjuvant therapy for locally advanced pancreatic cancer, where a circumferential level-III dissection around the arteries in combination with venous resection is frequently necessary [66].

65.3.4 Vascular Resections

Vascular resections are important techniques to increase radicality in pancreatic cancer surgery and are topic of a separate chapter in this book. While the first venous resection was already reported in 1927 [15], vascular resections were popularized much later. Again, Japanese surgeons had a leading role in introducing venous resections in common practice for pancreatic surgery [67]. Nowadays 30% and more of pancreatic resections for cancer involve venous resections and there is sufficient evidence that venous resections can be performed with adequate safety and

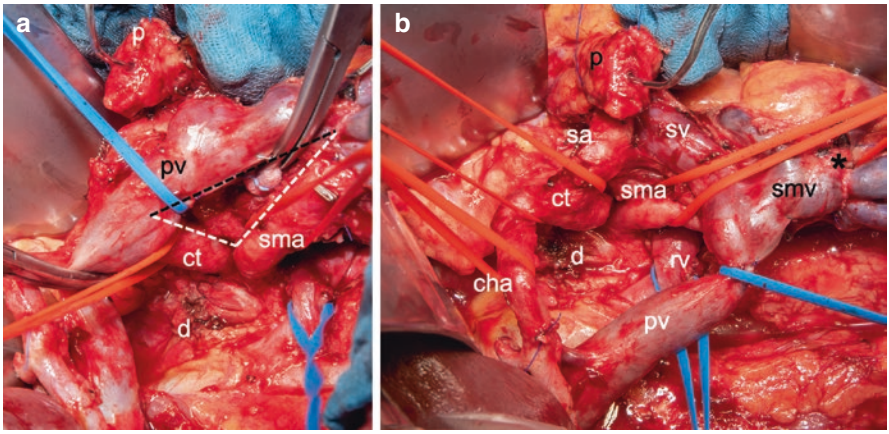

Fig. 65.2 Extended dissection of putatively tumor-infiltrated soft tissue (TRIANGLE). (**a**) Triangle bordered by the portal vein (pv), celiac trunk (ct), and superior mesenteric artery (sma). *d* right crus of diaphragm, *p* pancreas. (**b**) Surgical field after vessel-oriented pancreatic head resection. *cha* common hepatic artery, *ct* celiac trunk, *d* right crus of diaphragm, *p* pancreas, *pv* portal vein, *sa* splenic artery, *sma* superior mesenteric artery, *smv* superior mesenteric vein. Asterisk indicates site end-to-end reconstruction of the smv. (Reproduced with permission from Schneider M, Strobel O, Hackert T, Büchler MW. Pancreatic resection for cancer-the Heidelberg technique. Langenbecks Arch Surg. 2019 Dec;404 (8):1017–1022)

long-term outcomes [44, 68]. In contrast, arterial resections remain highly controversial, although they are increasingly applied in dedicated high-volume centers. Due to high morbidity and poor long-term outcomes, a strategy of neoadjuvant therapy is recommended whenever an arterial infiltration is suspected.

While some decades ago, pancreatic surgeons tried to avoid the vessels, the modern pancreatic resection techniques are oriented at the vessels as a common strategy. The result of any resection for pancreatic cancer should, therefore, look similar and include an exposure of the superior mesenteric, celiac and hepatic arteries consistent with a Level-III dissection and a TRIANGLE operation [65, 66, 69].

65.4 Current Trends and Future Directions

Research in pancreatic cancer surgery is currently dominated by several trends and controversies. New evidence in these "**Hot-topics and future research frontiers**" areas (Box 65.1) will define the future evolution of pancreatic cancer surgery. In research on perioperative management and outcomes, the quest for better strategies for prevention and management of postoperative pancreatic fistula remains in the focus. Treatment strategies that are adapted to the risk of postoperative pancreatic fistula as determined by recently developed scores may contribute to solve this persisting problem [70].

Box 65.1 Future Research Frontiers
Improvement of perioperative outcomes:

- Strategies to reduce the rate of postoperative pancreatic fistula.
- (Pancreatic Fistula-) risk-adapted treatment strategies.

Surgical technique:

- Effects of radical resection techniques on short and long term outcomes.
- Effects of minimally invasive pancreatic resections on short and long term outcomes.
- Role of vascular resections following neoadjuvant therapy.

Multimodal cancer therapy:

- Therapy sequencing (surgery first or neoadjuvant strategy) in resectable and borderline-resectable cancers.
- Role of "conversion surgery" in responders with unresectable and oligometastatic tumors.
- Novel regimens for neoadjuvant and adjuvant therapy.
- Role of radiotherapy.
- Role of locally ablative procedures in unresectable pancreatic cancer.

Patient selection and personalized therapy:

- New biomarkers for prediction of prognosis and therapy response.
- Better diagnostic tools for prediction of local resectability and detection of small metastases.
- Tailored therapy sequencing.
- Role of personalized oncology.
- Role of surgery in localized recurrence.

65.4.1 Minimal Invasive and Maximal Invasive Surgery

The evolution of surgical techniques is driven by two main trends that will dominate the next decades: On the one hand, there is a trend towards improving efficacy of pancreatic cancer surgery by extending resections towards more radical resections including vascular resection. This is closely linked to the trend to extend the indications for resections towards locally advanced, previously unresectable tumors after downstaging by neoadjuvant therapy. On the other hand we have a trend towards minimally invasive (laparoscopic and robotic) resections for pancreatic cancer [71–73].

The further evolution of pancreatic cancer surgery in these two main directions will in the end depend on their short and long-term outcomes. The current limited evidence suggests that minimally invasive distal pancreatectomy for cancer is safe and may be effective [73]. In contrast, minimally invasive pancreatoduodenectomy is much more technically demanding and may not be safe unless a long learning curve has been passed [74, 75]. One possible development is that the minimally invasive technique will become the new standard for left resections but will remain restricted to a few highly specialized surgeons for pancreatoduodenectomy.

65.4.2 Multimodal Treatment

Pancreatic cancer requires a multimodal treatment and the other important developments will occur in this context. One of the most pressing questions is on therapy sequencing in resectable and borderline-resectable pancreatic cancer. Based on heavily biased retrospective studies there is a current discussion about “neoadjuvant therapy for everybody”. Scientifically, we need to compare the strategies of surgery first vs. neoadjuvant therapy in randomized controlled trials with an intention-to-treat analysis [3]. While several such trials are ongoing, the first results of two trials are frequently used to support the neoadjuvant strategy while they only show how difficult it is to design and conduct a good trial in this area [76]. Preoperative staging and patient selection remain main challenges for such trials pointing to the fact that

better diagnostic tools are urgently needed. Two other seemingly opposing trends that are of relevance for the multimodal treatment of pancreatic cancer are (1) the standardized treatment of all patients along guidelines versus (2) personalized cancer medicine. Based on novel tools for evaluating prognosis and therapy response personalized medicine for pancreatic cancer in the future should not only include targeted drug therapy, but also personalized surgery and personalized therapy sequencing.

65.5 Conclusions

Pancreatic cancer surgery has enormously advanced in the last four decades and continues to rapidly evolve. Surgical resection remains the cornerstone of curatively intended therapy for pancreatic cancer. More effective systemic therapy regimens for the adjuvant and neoadjuvant settings have led to considerable improvements in long-term outcomes and an extension of the patient population eligible for surgical resection. We expect that with further advances in both surgical technique and medical treatment the role of surgery in the treatment of pancreatic cancer will further increase.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
3. Strobel O, Neoptolemos J, Jager D, Buchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2019;16(1):11–26.
4. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022.
5. Huang L, Jansen L, Balavarca Y, Molina-Montes E, Babaei M, van der Geest L, et al. Resection of pancreatic cancer in Europe and USA: an international large-scale study highlighting large variations. Gut. 2019;68(1):130–9.
6. Swords DS, Mulvihill SJ, Brooke BS, Stoddard GJ, Firpo MA, Scaife CL. County-level variation in use of surgery and cancer-specific survival for stage I–II pancreatic adenocarcinoma. Ann Surg. 2019.
7. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015;27(4):332–48.
8. Schnelldorfer T, Adams DB, Warshaw AL, Lillemoe KD, Sarr MG. Forgotten pioneers of pancreatic surgery: beyond the favorite few. Ann Surg. 2008;247(1):191–202.
9. Witzel O. Aus der Klinik des Herrn Prof. Trendelenburg. Beiträge zur Chirurgie der Bauchorgane. Deutsche Zeitschrift für Chirurgie. 1886;24:326–54.
10. Dal Monte B. Rendiconto statistico della sezione chirurgica dell' Ospedale d'Imola, anno 1898. Imola: Galeati; 1899.
11. Halsted W. Contributions to the surgery of the bile passages, especially of the common bile-duct. Bost Med Surg J. 1899;141:645–54.

12. Desjardins A. Technique de la Pancréatectomie. Rev Chir. 1907;35:945–73.
13. Kausch W. Das Carcinom der Papilla duodeni und seine radikale Entfernung. Beitr Klin Chir. 1912;78:439–86.
14. Hirschel G. Die resektion des Duodenums mit der Papille wegen Karzinoms. München Med Wochenschr. 1914;61:1728–9.
15. Gordon-Taylor G. The radical surgery of cancer of the pancreas. Ann Surg. 1934;100(1):206–14.
16. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg. 1935;102(4):763–79.
17. Brunschwig A. Resection of head of pancreas and duodenum for carcinoma—pancreatoduodenectomy. CA Cancer J Clin. 1974;24(6):363–7.
18. Whipple AO. A reminiscence: pancreaticduodenectomy. Rev Surg. 1963;20:221–5.
19. Priestley JT, Comfort MW, Radcliffe J. Total pancreatectomy for hyperinsulinism due to an islet-cell adenoma: survival and cure at sixteen months after operation presentation of metabolic studies. Ann Surg. 1944;119(2):211–21.
20. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. Surg Endosc. 1994;8(5):408–10.
21. Lillemoe KD, Rikkers LF. Pancreaticoduodenectomy: the golden era. Ann Surg. 2006;244(1):16–7.
22. Crile G Jr. The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. Surg Gynecol Obstet. 1970;130(6):1049–53.
23. Shapiro TM. Adenocarcinoma of the pancreas: a statistical analysis of biliary bypass vs Whipple resection in good risk patients. Ann Surg. 1975;182(6):715–21.
24. Harken AH. Presidential address: natural selection in university surgery. Surgery. 1986;100(2):129–33.
25. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg. 1990;211(4):447–58.
26. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006;244(1):10–5.
27. Fernandez-del Castillo C, Morales-Oyarvide V, McGrath D, Wargo JA, Ferrone CR, Thayer SP, et al. Evolution of the Whipple procedure at the Massachusetts General Hospital. Surgery. 2012;152(3 Suppl 1):S56–63.
28. Fernandez-del Castillo C, Sarr MG, Andrew L, Warshaw MD. Modern pioneer of pancreatic surgery. Surgery. 2012;152(3 Suppl 1):S1–3.
29. Gordon TA, Bowman HM, Tielsch JM, Bass EB, Burleyson GP, Cameron JL. Statewide regionalization of pancreaticoduodenectomy and its effect on in-hospital mortality. Ann Surg. 1998;228(1):71–8.
30. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346(15):1128–37.
31. Warshaw AL, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. Am J Surg. 1986;151(1):76–80.
32. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899–903.
33. Todd KE, Gloor B, Lane JS, Isacoff WH, Reber HA. Resection of locally advanced pancreatic cancer after downstaging with continuous-infusion 5-fluorouracil, mitomycin-C, leucovorin, and dipyridamole. J Gastrointest Surg. 1998;2(2):159–66.
34. Neoptolemos JP, Kerr DJ, Beger H, Link K, Pederzoli P, Bassi C, et al. ESPAC-1 trial progress report: the European randomized adjuvant study comparing radiochemotherapy, 6 months chemotherapy and combination therapy versus observation in pancreatic cancer. Digestion. 1997;58(6):570–7.
35. Krautz C, Nimptsch U, Weber GF, Mansky T, Grutzmann R. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg. 2018;267(3):411–7.
36. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8–13.

37. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584–91.
38. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761–8.
39. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an international study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20–5.
40. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the international study group on pancreatic surgery. Surgery. 2017;161(2):365–72.
41. Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet. 2011;377(9776):1514–22.
42. Keck T, Wellner UF, Bahra M, Klein F, Sick O, Niedergethmann M, et al. Pancreatogastrostomy versus pancreatojejunostomy for RECOnstruction after PANCreatoduodenectomy (RECOPANC, DRKS 00000767): perioperative and long-term results of a multicenter randomized controlled trial. Ann Surg. 2016;263(3):440–9.
43. Hartwig W, Hackert T, Hinz U, Hassenpflug M, Strobel O, Buchler MW, et al. Multivisceral resection for pancreatic malignancies: risk-analysis and long-term outcome. Ann Surg. 2009;250(1):81–7.
44. Hartwig W, Gluth A, Hinz U, Koliogiannis D, Strobel O, Hackert T, et al. Outcomes after extended pancreatectomy in patients with borderline resectable and locally advanced pancreatic cancer. Br J Surg. 2016;103(12):1683–94.
45. Strobel O, Berens V, Hinz U, Hartwig W, Hackert T, Bergmann F, et al. Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. Surgery. 2012;152(3 Suppl 1):S33–42.
46. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: neoadjuvant therapy with Folfirinox results in resectability in 60% of the patients. Ann Surg. 2016;264(3):457–63.
47. Michelakos T, Pergolini I, Castillo CF, Honselmann KC, Cai L, Deshpande V, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2017;269(4):733–40.
48. Fritz S, Klauss M, Bergmann F, Strobel O, Schneider L, Werner J, et al. Pancreatic main-duct involvement in branch-duct IPMNs: an underestimated risk. Ann Surg. 2014;260(5):848–55; discussion 55–6.
49. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88.
50. Hartwig W, Vollmer CM, Fingerhut A, Yeo CJ, Neoptolemos JP, Adham M, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the international study Group for Pancreatic Surgery (ISGPS). Surgery. 2014;156(1):1–14.
51. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the international study group on pancreatic surgery (ISGPS). Surgery. 2014;156:591–600.
52. Asbun HJ, Conlon K, Fernandez-Cruz L, Friess H, Shrikhande SV, Adham M, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the international study Group of Pancreatic Surgery. Surgery. 2014;155(5):887–92.
53. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. Pancreatic anastomosis after pancreatoduodenectomy: a position statement by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161(5):1221–34.

54. Dasari BV, Pasquali S, Vohra RS, Smith AM, Taylor MA, Sutcliffe RP, et al. Extended versus standard lymphadenectomy for pancreatic head Cancer: meta-analysis of randomized controlled trials. J Gastrointest Surg. 2015;19(9):1725–32.
55. Hartwig W, Gluth A, Hinz U, Bergmann F, Spronk PE, Hackert T, et al. Total pancreatectomy for primary pancreatic neoplasms: renaissance of an unpopular operation. Ann Surg. 2015;261(3):537–46.
56. Niesen W, Hank T, Buchler M, Strobel O. Local radicality and survival outcome of pancreatic cancer surgery. Ann Gastroenterol Surg. 2019;3(5):464–75.
57. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol. 2008;15(6):1651–60.
58. Strobel O, Hank T, Hinz U, Bergmann F, Schneider L, Springfeld C, et al. Pancreatic cancer surgery: the new R-status counts. Ann Surg. 2017;265(3):565–73.
59. Hank T, Hinz U, Tarantino I, Kaiser J, Niesen W, Bergmann F, et al. Validation of at least 1 mm as cut-off for resection margins for pancreatic adenocarcinoma of the body and tail. Br J Surg. 2018;105(9):1171–81.
60. Sanjay P, Takaori K, Govil S, Shrikhande SV, Windsor JA. 'Artery-first' approaches to pancreatoduodenectomy. Br J Surg. 2012;99(8):1027–35.
61. Nakao A, Takagi H. Isolated pancreatectomy for pancreatic head carcinoma using catheter bypass of the portal vein. Hepatogastroenterology. 1993;40(5):426–9.
62. Ironside N, Barreto SG, Loveday B, Shrikhande SV, Windsor JA, Pandanaboyana S. Meta-analysis of an artery-first approach versus standard pancreatoduodenectomy on perioperative outcomes and survival. Br J Surg. 2018;105(6):628–36.
63. Sabater L, Cugat E, Serrablo A, Suarez-Artacho G, Diez-Valladares L, Santoyo-Santoyo J, et al. Does the artery-first approach improve the rate of R0 resection in pancreatoduodenectomy?: a multicenter, randomized, controlled trial. Ann Surg. 2019;270(5):738–46.
64. Hirono S, Kawai M, Okada KI, Fujii T, Sho M, Satoi S, et al. MAPLE-PD trial (Mesenteric Approach vs. Conventional Approach for Pancreatic Cancer during Pancreaticoduodenectomy): study protocol for a multicenter randomized controlled trial of 354 patients with pancreatic ductal adenocarcinoma. Trials. 2018;19(1):613.
65. Inoue Y, Saiura A, Yoshioka R, Ono Y, Takahashi M, Arita J, et al. Pancreatoduodenectomy with systematic mesopancreas dissection using a supracolic anterior artery-first approach. Ann Surg. 2015;262(6):1092–101.
66. Hackert T, Strobel O, Michalski CW, Mihaljevic AL, Mehrabi A, Muller-Stich B, et al. The TRIANGLE operation—radical surgery after neoadjuvant treatment for advanced pancreatic cancer: a single arm observational study. HPB (Oxford). 2017;19(11):1001–7.
67. Nakase A, Matsumoto Y, Uchida K, Honjo I. Surgical treatment of cancer of the pancreas and the periampullary region: cumulative results in 57 institutions in Japan. Ann Surg. 1977;185(1):52–7.
68. Murakami Y, Satoi S, Motoi F, Sho M, Kawai M, Matsumoto I, et al. Portal or superior mesenteric vein resection in pancreatoduodenectomy for pancreatic head carcinoma. Br J Surg. 2015;102(7):837–46.
69. Schneider M, Strobel O, Hackert T, Buchler MW. Pancreatic resection for cancer-the Heidelberg technique. Langenbecks Arch Surg. 2019;404(8):1017–22.
70. Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, et al. Alternative fistula risk score for pancreatoduodenectomy (a-FRS): design and international external validation. Ann Surg. 2019;269(5):937–43.
71. de Rooij T, Lu MZ, Steen MW, Gerhards MF, Dijkgraaf MG, Busch OR, et al. Minimally invasive versus open pancreatoduodenectomy: systematic review and meta-analysis of comparative cohort and registry studies. Ann Surg. 2016;264(2):257–67.
72. Klompmaker S, van Hilst J, Wellner UF, Busch OR, Coratti A, D'Hondt M, et al. Outcomes after minimally-invasive versus open pancreatoduodenectomy: a pan-European propensity score matched study. Ann Surg. 2020;271(2):356–63.

73. van Hilst J, de Rooij T, Klompmaker S, Rawashdeh M, Aleotti F, Al-Sarireh B, et al. Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched study. Ann Surg. 2019;269(1):10–7.
74. van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol Hepatol. 2019;4(3):199–207.
75. Strobel O, Buchler MW. Laparoscopic pancreatoduodenectomy: safety concerns and no benefits. Lancet Gastroenterol Hepatol. 2019;4(3):186–7.
76. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268:215–22.

Part VIII
Complications After Pancreatic Surgery

Chapter 66
Chyle Leak After Pancreatic Surgery

Salvatore Paiella, Gabriella Lionetto, and Roberto Salvia

Take Home Messages

- Chyle leak is defined as an output of milky-like fluid from a drain, drain site, or wound that occurs 3 days or more postoperatively, with a triglyceride content ≥110 mg/dL (≥1.2 mmol/L).
- Three grades of severity (A, B, C) exist and are defined according to the management required and the postoperative impact.
- The mainstay of treatment is conservative management with dietary measures, including a diet high in protein, low in fat, and containing main-chain-triglycerides (MCT) or total parenteral nutrition (TPN) which is intended to decrease the flow of lymph.
- Interventional procedures are reserved for refractory cases as they are anecdotal and hardly effective.

Pearls and Pitfalls

- After a pancreatic resection, whenever the output of a drain turns out to be milky, it should be tested for triglycerides to facilitate early detection and diagnosis of a chyle leak.
- Treatment should be protracted until the resolution, i.e. when the drainage output become unequivocally limpid after the reintroduction of normal oral feeding. A conservative management should always be the first therapeutic option.

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- Surgical strategy—such as extended lymphadenectomy or vascular resection—may affect the risk of this complication.
- The presence of a chyle leak can be made at time of suspicion by testing for triglyceride content, the severity however is only made in retrospect.

Future Perspectives
- The widespread use of neoadjuvant treatment with more complex surgical procedures for pancreatic cancer could increase the incidence of chyle leak.
- Understanding structural alterations on peripancreatic tissue (including lymphatic vessels) induced by chemo/radiotherapy could help to prevent and treat such complications, as well as to clarify the pathogenesis.
- The early enteral feeding is one of the key factor of the enhanced recovery pathways after pancreatic surgery. At the same time its role in triggering the development of chyle leak is well-documented. Thus, establishing early optimal therapeutic reactive strategies within enhanced postoperative recovery pathways in case of a chyle leak is of utmost importance to ensure rapid postoperative recovery, and proper nutritional support.

66.1 Introduction

Chyle leak is an uncommon yet potentially important complication of pancreatic surgery. A chyle leak may occur as the consequence of a direct surgical lesion to the *cisterna chyli* or one of its major tributary lymphatic vessels [1]. These structures are located anterior to the first and second vertebrae at the same level as the pancreatic head and neck [2] making them more likely to be injured by dissection performed during pancreatic resections, especially those including extended lymph node dissections which are performed as a radical treatment option [3]. The first description of a chyle leak can be traced back to the seventeenth century when Gaspare Asellio observed white creamy-like effluvium after transecting a whitish cordon spreading through the mesentery during a dog autopsy mistaking it for a nerve.

66.1.1 Frequency of Chyle Leak After Pancreatic Surgery

The reported incidence of this postoperative complication varies widely (1–16%) mainly due to heterogenous definitions [4]. Among the more recent and larger series, Kuboki [5] reported 3.3% after pancreatoduodenectomy and 3.8% after distal resections in a series of more than 2000 patients. In a German series, Strobel reported an overall frequency at 10.4% in a series over 3300 patients [6], with highest rate in distal resections 16%. A series from Johns Hopkins found only 1.3% chyle leak in a series over 3500 pancreatic operations [7].

Table 66.1 ISGPS grading system for isolated chyle leak after pancreatic resection [5]

	Grade A	Grade B	Grade C
Therapeutic consequence	None or oral dietary restriction[a]	Nasoenteral nutrition with dietary restriction[a] and/or TPN, percutaneous drainage by IR, maintenance of surgical drains, or drugs (e.g. octreotide) treatment	Other invasive in-hospital treatment[b], admission to the ICU, and/or mortality[c]
Discharge with (surgical) drain or readmission	No	Possibly	Possibly
Prolonged hospital stay	No	Yes	Yes

TPN total parenteral nutrition, *IR* interventional radiology
[a]No-fat diet with/without medium-chain triglyceride
[b]Interventional radiology (lymphatic embolization/sclerosis) or reoperation
[c]Related directly to the chyle leak

66.1.2 Definition of Chyle Leak

The International Study Group of Pancreatic Surgery (ISGPS) has recently released a consensus statement with a definition and grading system of chyle leak to allow valid assessments and comparison of studies from different settings. According to this, a chyle leak is defined as "*as output of milky-colored fluid from a drain, drain site, or wound on or after postoperative day 3, with a triglyceride content ≥110 mg/dL (≥1.2 mmol/L)",* with the grading system outlined in Table 66.1 [4].

The validity of this classification was confirmed by the authors who demonstrated that, in addition to the length of stay, the rate of major complications, and the occurrence of septic events, the average cost of hospitalization also differed between the three grades [8].

The findings of all major surgical series exploring the incidence and risk factors of chyle leak are outlined in Table 66.2.

Unfortunately, these studies were reported before the ISGPS consensus statement, and they come from heterogeneous retrospective surgical cohorts. Fundamental parameters, such as the diagnostic criteria, differ between series, as well as the type of surgery associated with chyle leak. This may explain the incongruity in the reported incidence of this complication according to different reports, and the different management pathways adopted.

66.1.3 Risk Factors

Several factors that independently increase the risk of developing chyle leak have been reported. They are showed in Table 66.3.

In general, the alterations and tissue distortions induced by a chronic process (such as in chronic pancreatitis or diabetes) or locally by neoadjuvant treatments (such as in malignancy) could increase the risk of lymphatic rupture and chyle leak [6, 10].

Table 66.2 Overview of major series investigating chyle leak after pancreatic surgery

Study	Pts	Incidence of chyle leak, %	Time of onset (days)	Management (%)	Risk factors
Malik [9]	105	6.7	6 (5–37)	TPN SS PV shunt	Early enteral feeding
Assumpcao [7]	3532	1.3	5 (4–8)	TPN SS Lscint /Lgram Reoperation	Longer operative time; No. of lymph nodes harvested; Vascular resection
Van der Gaag [10]	609	11	6 (3–52)	LCT diet TPN Expectative approach	Female gender; Focal chronic pancreatitis
Aoki [11]	65	7.7	8 (6–16)	TPN SS	Not reported
Noji [12]	138	8	NA	5 days fasting + TPN	Early enteral feeding
Kim [13]	222	10.8	5 (3–9)	TPN Diet No treatment	Early enteral feeding
Abu Hilal [7]	245	16.3	4–7	MCT diet	Extensive lymphadenectomy; Postoperative portal/mesenteric venous thrombosis; Early enteral feeding
Kuboki [5]	574	3	NA	TPN alone SS	Manipulating para-aortic area; Vascular resection; Early enteral feeding
Pan [11]	1921	2.6	NA	NA	Manipulating para-aortic area and superior mesenteric artery root area; Retroperitoneal invasion; Focal chronic pancreatitis; Early enteral feeding
Strobel [6]	3324	10.4	5 (3–8)	MCT TPN MCT + SS TPN + SS MCT diet + TPN + SSA No specific therapy	Pre-existing diabetes; Resection for malignancy; Longer operative time; Duration of surgery; Concomitant POPF/abscess
Paiella [8]	945	4.5	NA	LCT diet Switch to TPN TPN ab initio	*Overall*: Younger age *Grade B only*: Preoperative biliary drain; Pancreatoduodenectomy; High estimated blood loss; Longer operative time

TPN total parenteral nutrition, *SS/SSA* somatostatin/somatostatin analogues, *PV* peritoneovenous, *Lscint* lymphoscintigraphy, *Lgram* lymphangiogram, *LCT/MCT* low/middle-chain-triglycerides

Table 66.3 Risk factors for chyle leak after pancreatic surgery

Pre-operative factors	Intra-operative factors	Post-operative factors
• Female sex	• Dissection of the para-aortic/ superior mesenteric artery root area	• Early enteral feeding
• Age	• Extended lymphadenectomy and total number of lymph nodes harvested	• Concomitant post-operative pancreatic fistula or abdominal abscess
• Pre-existing diabetes	• Presence of retroperitoneal invasion	• Portal vein/superior mesenteric vein thrombosis
	• Chronic pancreatitis	
	• Resection for malignancy	
	• Vascular resection and reconstruction	
	• Longer operative time	

An early enteral intake has been considered the most important risk factor for chyle leak. This is attributed to the stimulation operated by the lipid content of the food that keeps open the disrupted lymphatic vessels before they have time to heal following surgery [9]. Physiologically, flow through the cisterna chyli increases from a fasting baseline of <1 mL up to 225 mL/min after ingestion of a fatty meal.

66.1.4 Intraoperative Detection and Tests

Several investigators have developed different techniques to detect the leak directly in the operating theatre. They do this by delivering fat-containing fluid to the duodenum, either by administering 60 mg of butter 4 h prior to surgery by injecting 50 mL of 10% intralipid solution into the jejunum prior to its division, or by delivering 100 mL of milk via a naso-gastric tube into the duodenum (the so called "milky test"). Using this system Aoki et al. demonstrated that most lymphatic leakage sites lie around the periphery of the superior mesenteric artery and vein area [12].

A lower incidence of chyle leak events after routine use of the milky test was suggested in their practice, despite a recent report downplaying its role in favour of sealing technology [13]. Interestingly, Assumpcao et al. found that for every extra 30 min of operative time, the risk of developing chyle leak increased by 14%. Similarly, for each individual lymph node harvested the risk of chyle leak increased by 6%, while vascular resection was the most strongly associated with an eightfold risk of developing a chyle leak [7].

66.2 Management of Chyle Leak After Pancreatic Surgery

At present there is no single, robust, evidence-based protocol for the management of a chyle leak. Treatment options include dietary measures, use of pharmacological agents (e.g. Somatostatin analogues), and surgical and percutaneous interventions in selected cases [4].

A brief summary of the authors' policy of management is shown in Fig. 66.1. When the output of drainage has the typical milky-like appearance, or if there is any doubt of a chylous component, fluid is sampled and analysed for triglycerides. When the level is ˃110 mg/dL from POD 3 on, then a diagnosis of chyle leak is established (according to ISGPS consensus statement), irrespective of the levels of amylase of the fluid.

Management is tailored according to different clinical scenarios. If the leak has been diagnosed after the start of oral feeding, then a low-fat diet is administered at first. If ineffective, standard total parenteral nutrition is administered. Conversely, the first-line treatment would be total parenteral nutrition (especially if concomitant delayed gastric emptying is present). In rare case of failure of conservative treatments, after up to 4–6 weeks of total parenteral nutrition, a more aggressive treatment (such as percutaneous procedure or relaparotomy) is carefully evaluated, balancing the risk over the benefits. Indeed, in the authors' experience chyle leak solves almost always spontaneously, and interventions (including relaparotomy) may be technically demanding. The treatment continues until the drainage output becomes unequivocally limpid after the reintroduction of normal oral feeding, on a safe trial-and-error basis. We systematically do not treat chyle leak with enteral nutrition and we do not reassess the triglycerides levels to confirm biochemically the resolution of the leak. Also, treatment with somatostatin is not standardised and is carefully evaluated in each individual case. No changes are adopted if the fluid becomes rich in amylase, unless complications occur (basically abdominal collections, with systemic signs of inflammation/infection); total parenteral nutrition is continued and the output from the drainage monitored daily, drives the management, together with repeated evaluation of triglycerides and amylase. If then a chyle leak solves but a postoperative pancreatic fistula remains, the management is the one of the latter (enteral feeding and/or nihil per mouth, low-fat-diet).

66.2.1 Non-Interventional

The importance of conservative measures, with a success rate ranging from 75 to 85%, has been emphasized by several reports [6]. Dietary measures include a low-fat diet with restriction of long-chain triglycerides, a medium-chain triglycerides diet, and a fat-free diet. As medium-chain triglycerides are directly absorbed along the gut mucosa and transported as free fatty acids and glycerol directly into the portal circulation bypassing the lymph system, restricting a normal oral diet and

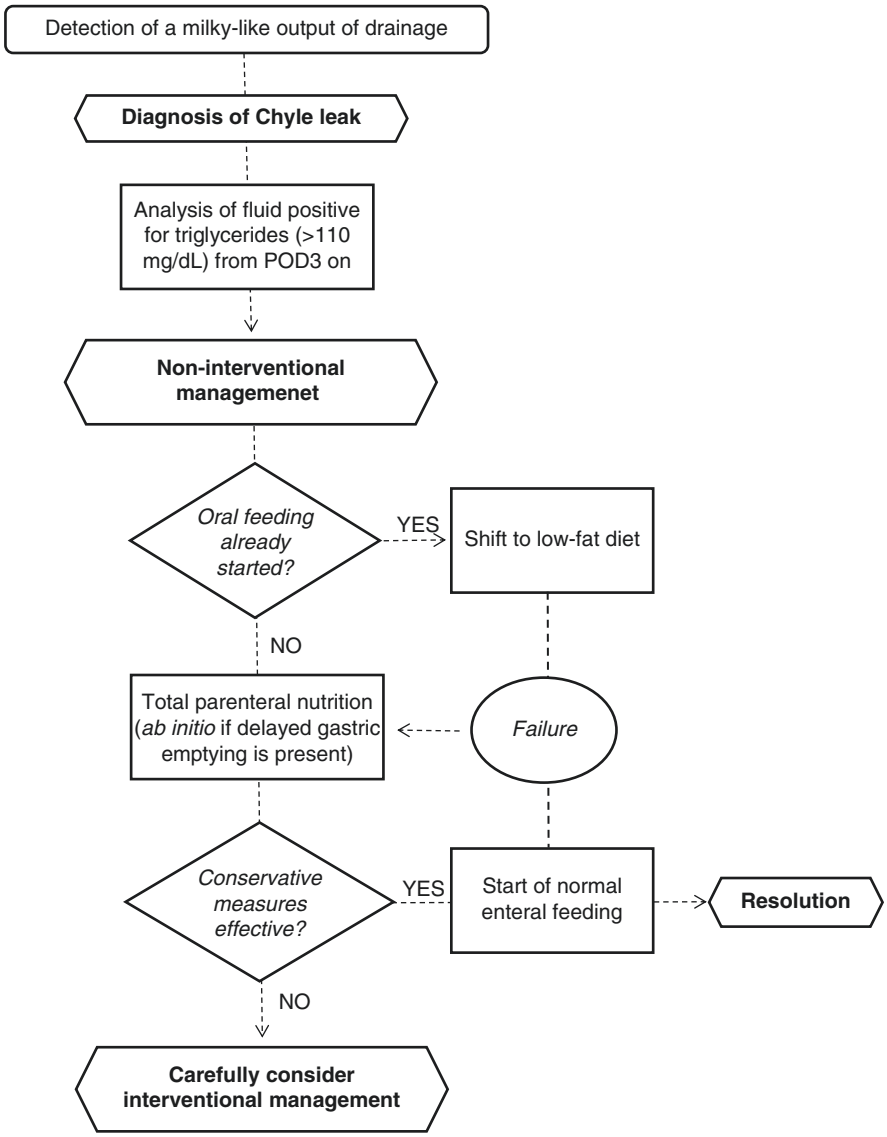

Fig. 66.1 Flowchart outlining key steps of chyle leak diagnosis and management at the authors' institution

replacing it with a medium- to -low chain triglyceride regimen has been suggested in patients at high risk of developing chyle leak [7, 14]. In the authors' experience some weeks may be necessary to obtain the healing of chyle leak with this method. In this case, a good communication with patient is fundamental, in order to explain the commonly low clinical burden of this complication, and the need of time to solve.

Treatment with somatostatin or somatostatin analogues may be another valid therapeutic option. Due its short half-life (1–3 min) somatostatin is usually administered intravenously, while octeotride has a longer half-life (~ 2 h) and can be administered by subcutaneous injection. The rationale beyond their usage is that they reduce lymph flow by decreasing the splanchnic blood flow and portal pressure and by reducing fat absorption in the bowel [15]. The latter effect depends mainly upon the inhibition of pancreatic exocrine function. Kuboki et al. [5] observed a significant decrease in the daily drainage output (to less than 100/mL day) 1 day after initiation of somatostatin analogues treatment, whereas the same effect was not seen in similar patients with chyle leak treated with total parenteral nutrition alone. In addition, patients treated with somatostatin analogues resumed oral intake sooner and their abdominal drains were removed earlier than patients in the total parenteral nutrition-alone group [5]. Total parenteral nutrition may provide adequate and complete nutritional needs, especially in those patients who are unable to tolerate oral intake (such as in those with delayed gastric emptying) or in whom nutritional requirements cannot be met by oral supplements alone [16]. In addition, chyle leak and its more diffuse counterpart, chylous ascites (or *chyloperitoneum*), may induce malnutrition and immunodepression via the loss of immunoglobulins and protein [1].

Nutritional support, provided by total parenteral nutrition in combination with somatostatin analogues (e.g. octreotide, administered subcutaneously at a dose of 100 μg three times a day), appears an effective therapy with a median duration of use of 7–8 days until resolution (in the absence of other complications) [9]. Drawbacks of total parenteral nutrition include potential complications related to the central route of administration (mainly infectious), failure to maintain gut mucosal integrity, and costs [16].

66.2.2 Interventional

Patients refractory to conservative management may require a more aggressive therapeutic approach [7], including lymphoscintigraphy and lymphangiogram [17], sclerotic embolization [18, 19], re-exploration for surgical ligation of leakage sites, and peritoneovenous/peritoneosubcutaneous shunt insertion [7, 14]. The efficacy of these complex interventions is reported mainly by small cohort studies and case reports [20]; thus, results are controversial. Another treatment option has been reported by Corradini et al. [21] and is based on clinical experience with lymphocutaneous fistulas. The authors described the successful use of low-dose radiotherapy (8.0 Gy administered in daily fraction of 1.0 Gy) in treating a patient with very refractory chylous ascites which developed following a pancreaticoduodenectomy for cancer.

66.3 Morbidity and Mortality

Controversy exist as regard the impact of chyle leak on postoperative outcome and survival. According to some studies, chyle leak is not associated with poor survival or an increased risk of surgical/general complications or a prolonged hospital stay [7, 14]. However, other reports show that patients with chyle leak do experience a prolonged duration of abdominal drainage and a longer hospital stay [14], and a poorer survival outcome.

When comparing the chyle leak group to patients with no leak, most of the complications reported in those with chyle leak did not occur with a higher frequency. The most frequently reported complications include malnutrition (defined as serum albumin less than 3.5 mg/dL) in 92%, sepsis (13%), peritonitis (6%), abscess (4%), and concomitant clinically-relevant pancreatic fistula (4%) [6].

In comparison to this, when comparing patients with a contained chyle leak to patients with a diffuse chylous ascites, the prognosis seems to be substantially different. Patients with chylous ascites have a protracted clinical course and a need for additional therapeutic interventions. Survival analysis showed worse long-term outcome in the chylous ascites group than the chyle leak one (3-year survival of 19% vs. 53%) [7].

In the largest cohort of patients reported so far, Strobel et al. [6] demonstrated that overall survival in patients with pancreatic cancer was not affected by the development of an isolated chyle leak. In subgroup analysis however, they identified failure of conservative management (defined as drain output of 2000 mL or greater after 14 days of treatment) to be associated with worse survival in patients with palliative resection (median survival of 5.2 months in patients with failed treatment vs. 16.4 months in patients whose chyle leak resolved) but not in patients who had potentially curative resections (median survival of 20.5 months vs. 23.8 months respectively). Thus, chyle leak, especially refractory chyle leak, has a potential negative effect on long-term outcome.

66.4 Conclusions

Chyle leak is a rare complication of pancreatic surgery that almost always responds well to non-operative measures and has a significant clinical and economic impact [8]. Unfortunately, available data are limited and derived from heterogeneous series. Hence no reliable conclusions can be drawn about early detection and treatment strategies. In our experience, adoption of the International Study Group of Pancreatic Surgery classification reliably and consistently identifies the different clinical scenarios of chyle leak, thus overcoming the lack of uniformity in reporting the actual incidence of this complication after pancreatic surgery.

References

1. Browse NL, Wilson NM, Russo F, et al. Aetiology and treatment of chylous ascites. Br J Surg. 1992;79:1145–50. https://doi.org/10.1002/bjs.1800791110.
2. Loukas M, Wartmann CT, Louis RG Jr, et al. Cisterna chyli: a detailed anatomic investigation. Clin Anat. 2007;20:683–8. https://doi.org/10.1002/ca.20485.
3. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156:591–600. https://doi.org/10.1016/j.surg.2014.06.016.
4. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the international study group on pancreatic surgery. Surgery. 2017;161:365–72. https://doi.org/10.1016/j.surg.2016.06.058.
5. Kuboki S, Shimizu H, Yoshidome H, et al. Chylous ascites after hepatopancreatobiliary surgery. Br J Surg. 2013;100:522–7. https://doi.org/10.1002/bjs.9013.
6. Strobel O, Brangs S, Hinz U, et al. Incidence, risk factors and clinical implications of chyle leak after pancreatic surgery. Br J Surg. 2017;104:108–17. https://doi.org/10.1002/bjs.10316.
7. Assumpcao L, Cameron JL, Wolfgang CL, et al. Incidence and management of chyle leaks following pancreatic resection: a high volume single-center institutional experience. J Gastrointest Surg. 2008;12:1915–23. https://doi.org/10.1007/s11605-008-0619-3.
8. Paiella S, De Pastena M, Casciani F, et al. Chyle leak after pancreatic surgery: validation of the International Study Group of Pancreatic Surgery classification. Surgery. 2018;164:450–4. https://doi.org/10.1016/j.surg.2018.05.009.
9. Malik HZ, Crozier J, Murray L, et al. Chyle leakage and early enteral feeding following pancreatico-duodenectomy: management options. Dig Surg. 2007;24:418–22. https://doi.org/10.1159/000108324.
10. van der Gaag NA, Verhaar AC, Haverkort EB, et al. Chylous ascites after pancreaticoduodenectomy: introduction of a grading system. J Am Coll Surg. 2008;207:751–7. https://doi.org/10.1016/j.jamcollsurg.2008.07.007.
11. Pan W, Yang C, Cai SY, et al. Incidence and risk factors of chylous ascites after pancreatic resection. Int J Clin Exp Med. 2015;8:4494–500.
12. Aoki H, Takakura N, Shiozaki S, et al. Milk-based test as a preventive method for chylous ascites following pancreatic resection. Dig Surg. 2010;27:427–32. https://doi.org/10.1159/000320692.
13. Aoki H, Utsumi M, Sui K, et al. Changes over time in milk test results following pancreatectomy. World J Gastrointest Surg. 2016;8:246–51. https://doi.org/10.4240/wjgs.v8.i3.246.
14. Abu Hilal M, Layfield DM, Di Fabio F, et al. Postoperative chyle leak after major pancreatic resections in patients who receive enteral feed: risk factors and management options. World J Surg. 2013;37:2918–26. https://doi.org/10.1007/s00268-013-2171-x.
15. Creutzfeldt W, Lembcke B, Folsch UR, et al. Effect of somatostatin analogue (SMS 201–995, Sandostatin) on pancreatic secretion in humans. Am J Med. 1987;82:49–54. https://doi.org/10.1016/0002-9343(87)90426-8.
16. Gianotti L, Besselink MG, Sandini M, et al. Nutritional support and therapy in pancreatic surgery: A position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018;164:1035–48. https://doi.org/10.1016/j.surg.2018.05.040.
17. D'Hondt M, Foubert K, Penninckx F, et al. Lymphangiography as a treatment method for chylous ascites following pancreaticoduodenectomy. J Gastrointest Cancer. 2011;42:272–4. https://doi.org/10.1007/s12029-010-9240-2.
18. Cope C. Diagnosis and treatment of postoperative chyle leakage via percutaneous transabdominal catheterization of the cisterna chyli: a preliminary study. J Vasc Interv Radiol. 1998;9:727–34. https://doi.org/10.1016/s1051-0443(98)70382-3.

19. Kim J, Won JH. Percutaneous treatment of chylous ascites. Tech Vasc Interv Radiol. 2016;19:291–8. https://doi.org/10.1053/j.tvir.2016.10.006.
20. Kollmar O, Schilling MK, Buchler MW. Treatment of chyloperitoneum after extended lymphatic dissection during duodenopancreatectomy. Int J Pancreatol. 2000;27:83–7. https://doi.org/10.1385/IJGC:27:1:83.
21. Corradini S, Liebig S, Niemoeller OM, et al. Successful radiation treatment of chylous ascites following pancreaticoduodenectomy. Strahlenther Onkol. 2015;191:448–52. https://doi.org/10.1007/s00066-014-0805-z.

Chapter 67
Post-op Pancreatic Hemorrhage

O. Radulova-Mauersberger, J. Weitz, and M. Distler

Take Home Messages
- PPH is a feared complication after surgery associated with nearly one-half of the postoperative mortality.
- Sentinel bleeding occurs is almost 50% of patients with delayed PPH and requires immediate adequate management.

Pearls and Pitfalls
- Endovascular management should be performed as a first-line treatment in cases of delayed bleeding.
- In hemodynamically unstable patients, resuscitation should be attempted for performing interventional radiology.
- PPH may occur also due to radical lymphadenectomy and arterial anastomosis.
- Formation of pseudoaneurysms causes delayed PPH in most of the patients.
- The failure to rescue rate is much higher in low volume centers which may be due to the fact that Sentinel bleeding is not recognized and adequately managed.

Future Perspectives
- Risk-adjusted surgery and improving operative techniques is needed to prevent POPF as a major risk factor for late bleeding.
- An update of the ISGPS definition for PPH is required to focus on clinical relevant occurrence of postoperative pancreatic hemorrhage

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- Reevaluation of Grade A bleeding is required to avoid overestimation of PPH rates.
- Development of an internationally accepted and standardized algorithm of diagnostics and management of PPH.

67.1 Introduction

Perioperative mortality after pancreatic surgery has been remarkably reduced in the last years in high-volume centers to less than 5% [1–4], However, pancreatoduodenectomy is still associated with a high morbidity up to 50% [5–8]. Post-op pancreatic hemorrhage is a less common but severe complication and adequate management has always been a major concern for hepato-pancreato-biliary (HPB) surgeons. A more than sixfold increase in mortality compared to other postoperative complications in patients with PPH after surgery is reported [9] Until 2007 the published incidences varied remarkably due to a lack of reliable definition of PPH. Therefore, the international study group for pancreatic surgery (ISGPS), founded in 2006, provided an universally applicable definition of PPH. Postoperative hemorrhage was stratified into Grades A, B, and, C based on time of bleeding onset, location, and severity (Table 67.1).

Table 67.1 Adapted from Wente et al. Postpancreatectomy hemorrhage (PPH)–An International Study Group of Pancreatic Surgery (ISGPS) definition, Surgery 142(1): 20–25, 2007 [17]

Classification of PPH						
Grade	Time of onset	Location	Severity	Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early	Intra- or extraluminal	Mild	Well	Observation, blond count and, if necessary, computed tomography	No
B	Early or late	Intra- or extraluminal	Mild	Often well/ intermediate, very rarely lifethreatening	Observation, blond count, computed tomography, angiography, endoscopy	Transfusion of fluid, blood, intermediate care unit (or ICU), therapeutic endoscopy, embolization, relaparotomy for early PPH
C	Late	Intra- or extraluminal	Severe	Severely impaired, life-threatening	Angiography, computed tomography, endoscopy	Localization of bleeding, angiography and embolization, (endoscopy) or relaparatomy, ICU

67.1.1 Classification

According to the classification, early (within the first 24 h after index operation) and delayed (beyond the period of 24 h) hemorrhage are defined depending on the time of onset. Based on the intensity, events of bleeding are classified into mild (hemoglobin decrease less than 3 g/dL and no need of surgical or interventional angiographic procedures) and severe (hemoglobin decrease more than 3 g/dL, life-threatening, invasive rocedures are necessary). Grade A consists of all early mild bleedings and Grade C of all late severe events. Grade B contains the early severe and late mild bleeding occurrences. Based on the bleeding site, hemorrhage is classified into intra- and extraluminal.

Intraluminal bleeding originates mostly from the anastomotic sites, from the pancreatic cut surface and suture line of the pancreaticojejunostomy or from the duodeno- or gastrojejunostomy. Also stress ulcers can be an intraluminal source of bleeding after operation [8]. The extraluminal hemorrhage originates from peripancreatic vessels and pseudoaneurysms, or from resection surfaces in the operative field.

Most common bleeding sources are the stump of the gastroduodenal artery, followed by the common and proper hepatic artery, superior mesenteric artery, and other bleeding sites (Fig. 67.1) [8, 10].

67.1.2 Sentinel Bleeding

"Sentinel bleeding" is defined as a small amount of bloody drainage fluid, hematemesis or melena, which stops spontaneously yet is followed by a massive bleeding several hours later. In the Oxford English dictionary, sentinel is defined as "a soldier whose job is to guard something". In 1991 Brodsky and Turnbill first described the term of "sentinel bleeding" after pancreatoduodenectomy analogous to the surgical experience in cervical and inguinal lymphadenectomy. According to the authors, it

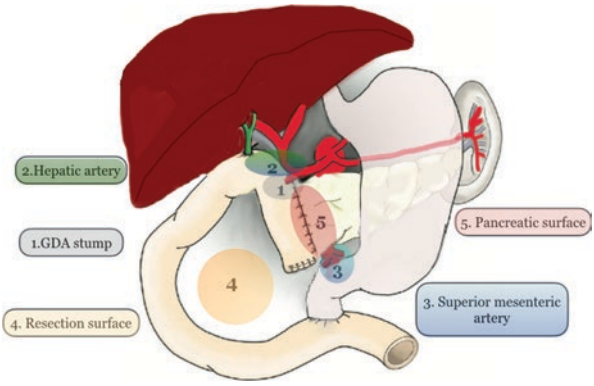

Fig. 67.1 Most likely sites of bleeding after pancreatic resection [8, 10]. (1) GDA (gastroduodenal artery) stump; (2) hepatic artery; (3) superior mesenteric artery (SMA); (4) resection surface; (5) pancreatic surface

is an indicator event for a massive following hemorrhage and, thus, its reliable recognition and adequate management is essential to prevent fatal outcomes [11]. Several authors describe the importance of this worrying event for preventing serious life -threatening episodes. Sentinel bleeding occurs in approximately 50–80% of the patient cohort for an average of 2,2 days before massive bleeding [12, 13].

The etiology of PPH is different depending on the time of onset. Early hemorrhage (<24 h) occurs generally due to technical surgical failure. Late bleeding (>24 h) is mostly caused by erosion due to an inflammatory process, like pancreatic fistula, or anastomotic dehiscence. Due to leakage of enzyme rich fluid in the abdomen, pancreatic fistula lead to arterial erosion and formation of pseudoaneurysms. A rupture of a pseudoaneurysm is the reason for severe late bleeding in one-third of cases and post-op hemorrhage is associated with pancreatic fistula in 80% of cases [14]. One potential mechanism might be the use of electrocautery and radical lymphadenectomy which affects the wall of the peripancreatic vessels and thus facilitates corrosion and vascular lesions [15, 16].

67.2 Incidence and Diagnostics

PPH occurs after 5–10% of all pancreatic resections, which is quite rare compared to other specific complications as delayed gastric emptying (19–57%) or POPF (3–45%) [8, 12, 15, 17–19]. Nevertheless, this complication is with 30–50% one of the main causes of mortality after pancreatic surgery [15]. Current studies published a sixfold increase in mortality for patients after PPH [9].

The clinical presentation of postoperative bleeding is very heterogenous.

Based on the ISGPS classification, few studies have published their results. Grade A bleeding, corresponding to mild early post-op hemorrhage, was mostly not recorded in databases and, thus generally not evaluated. The published incidence of 4.8%–12.7% for PPH Grade A is therefore based on only several publications [20, 21], meaning the estimated number of unreported cases might be higher. Grade B PPH occurred in 1.5–15.2% and Grade C PPH in 0.5–9.2% of patients after pancreatic surgery [8, 20, 22, 23].

Based on the ISGPS classification, algorithms of diagnostic and management were established.

Postoperative bleeding presents clinically as blood in the abdominal drains or melena, hematochezia or hematemesis along with clinical signs as hemoglobin dynamics, hypotension, tachycardia or even oliguria and hypovolemic shock.

The decision for further diagnostic management is based on one main aspect-**hemodynamic stability**.

The majority of patients undergoes a diagnostic investigation before intervention for PPH but in case of hemodynamic instability and massive hemorrhage regardless of timing of bleeding an emergent angiography or re-operation should be performed [12, 15].

Patients who are in relatively stable hemodynamic condition should undergo a triple-phase CT—angiography (unenhanced, arterial, and venous phases) as soon as the sentinel bleeding occurs [8, 24, 25]. Furthermore, computed tomography with angiography (CT-A) is a reliable tool for the detection of the site, cause and nature of bleeding. The procedure is widely available, fast and non-invasive, and very helpful to guide further treatment. The arterial phase shows the vessel anatomy and potential extravasation as origin of active arterial bleeding (Fig. 67.2). The venous phase can show a delayed contrast pooling which can be due to the filling of pseudoaneurysms [24]. Nevertheless, in 55% CT-A is not able to locate the origin of bleeding but some suspicious signs for PPH like hematoma or parietal irregularities of arteries might be found [26].

Earlier studies favored endoscopy for diagnosis of hematemesis, melena or, blood in the nasogastric tube as symptoms of gastro-intestinal intraluminal bleeding [27]. Current publications report that CT-A is superior to endoscopy for detecting site and etiology of gastro-intestinal hemorrhage [28]. It is also important to consider a possible extraluminal source that only presents as intraluminal bleeding in case of anastomotic failure, such as dehiscence of the pancreaticojejunostomy. Therefore, endoscopy may fail in detecting the bleeding source, or may be even dangerous in some cases of false positive findings of hemorrhage sources (like erosive gastritis) and hence delaying adequate intervention [19, 26].

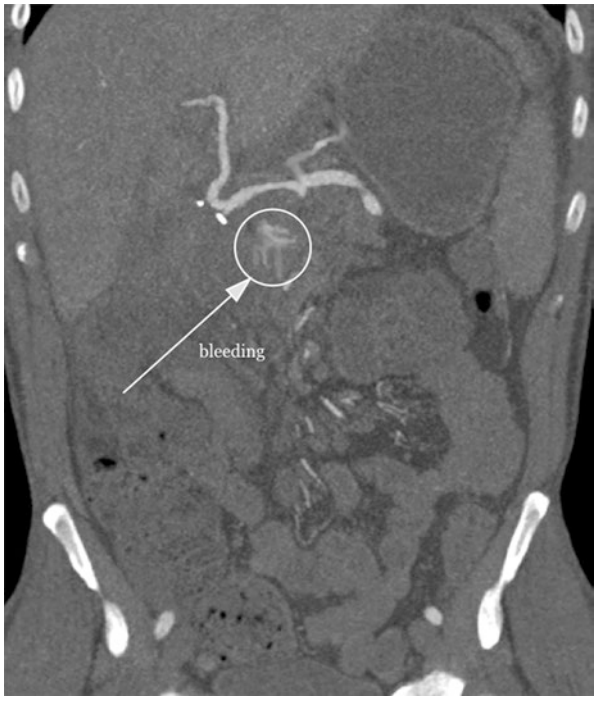

Fig. 67.2 Computer tomography with arteriography showing active bleeding from a branch of the superior mesenteric artery after pancreatoduodenectomy

If the site of bleeding is uncertain after CT-A, angiography of the celiac axis and superior mesenteric artery should be performed. Angiography can deliver additional information by detecting paravasation, vascular spasm, or other irregularities as indirect signs of hemorrhage. Although angiography appears to be a more specific and sensitive method, it still fails to identify bleeding in 25% of cases due to the intermittent nature of the hemorrhage [10]. If the hemorrhage source after sentinel bleeding remains unclear an intensive observation of the patient with hemodynamic monitoring and repeated blood test is strongly recommended.

67.3 Management

After establishing the ISGPS definition for PPH, some studies published an algorithm for management of bleeding, mostly based on retrospective data and small case series due to low incidence [8, 15]. Treatment procedures for PPH comprise endovascular intervention (angiography with coiling or stent grafting), endoscopy or surgery.

A suggested algorithm for diagnosis and treatment is shown in Fig. 67.3.

The strategy of PPH treatment should be generally stratified according to the nature of bleeding. The decision on the diagnostic and treatment procedure is based on two important facts: time of onset in relation to the index operation and hemodynamic status of the patient. Early severe hemorrhage may be intra- or extraluminal and usually due to insufficient hemostasis during surgery and can be successfully managed by surgical re-intervention. This may involve jejunotomy to manage bleeding at a pancreaticojejunostomy or surgical control of an extraluminal bleeding. Endoscopy represents another option of first-line management for intraluminal PPH. It can provide successful treatment of bleeding for anastomotic ulcers or patients with pancreatogastrostomy (PG) [29] but is only rarely suitable for early hemorrhage from the surface of the pancreatojejunostomy. Care must be taken not to delay clinical management of a bleeding pancreatojejunostomy by prolonged endoscopic maneuvers.

For late hemorrhage even small amounts of blood loss in the drainage or in the gastric tube should trigger diagnostic steps. After CT-A, angiography of the celiac axis and superior mesenteric artery, and consequently embolisation or stent-grafting as less invasive and highly effective technique should be performed. Interventional radiology gained enormous acceptance in the treatment of PPH in the last years and is now recommended as a first-line therapy for hemodynamic stable patients. Recent data show that endovascular treatment is associated with lower morbidity and mortality, lower blood loss and shorter intensive care unit stay than surgery. A success rate of 87% in achieving hemostasis is reported [12, 24]. Angiography may show the presence of pseudoaneurysms and active contrast extravasation while simultaneously providing a treatment option: mainly by embolisation and blocking the distal blood flow or stent grafting, ceasing the hemorrhage by preserving the distal blood flow [24]. In awareness of the bleeding locations after pancreatectomy,

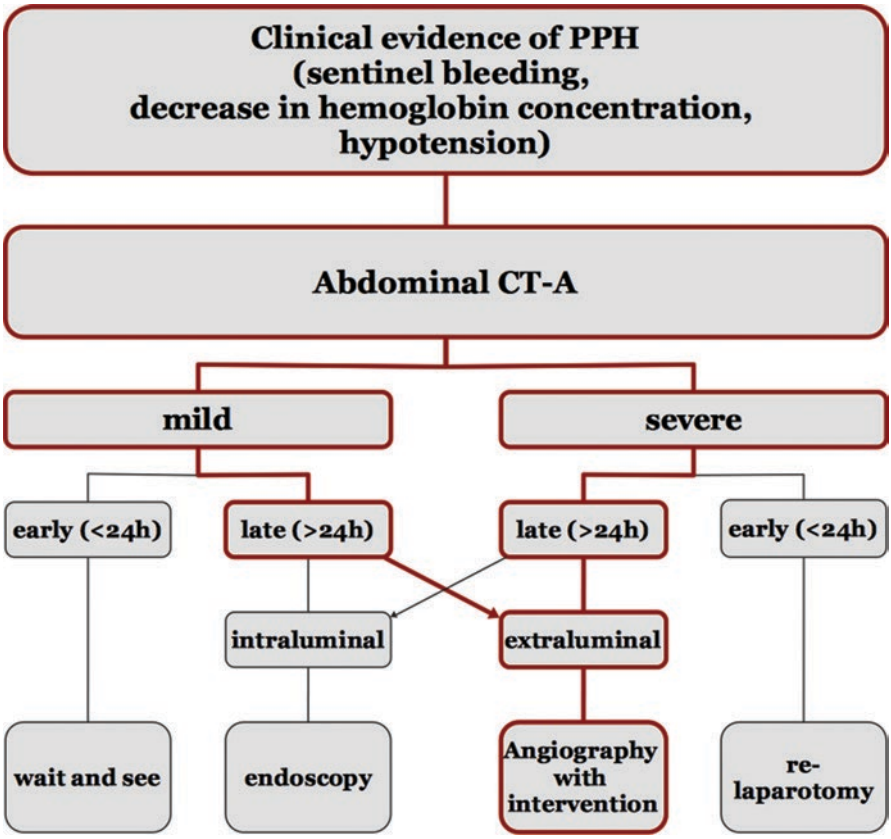

Fig. 67.3 Suggested algorithm for treatment of PPH. The most frequent steps are highlighted in red

coil-embolisation is often performed in the stump of the gastroduodenal artery or other small single feeding vessels. Stent grafting is the preferred procedure for erosions in the common and proper hepatic artery, celiac axis, or in the superior mesenteric artery preserving the distal perfusion [24] (Fig. 67.4).

Nevertheless, endovascular repair may fail to succeed and, in these cases, surgery is required to achieve control of the bleeding. Operative management can provide hemostasis by suturing the bleeding stump of small vessels, without blocking the blood flow of the feeding vessel. Furthermore, surgery may enable the control of local infection and sepsis by completion pancreatectomy or appropriate drainage placement and lavage. However, re-laparotomy for PPH may be complex because of postoperative adhesions and poor operative view due to massive bleeding. In such cases, an aortic occlusion balloon catheter may be helpful for controlling the hypovolemic shock and obtaining a better view of the operative field [13].

Surgery may be also performed additionally after providing control of bleeding by endovascular intervention for evacuating hematoma, abscess or salvage pancreatectomy for pancreatitis or dehiscence. If a patient is septic but hemodynamic

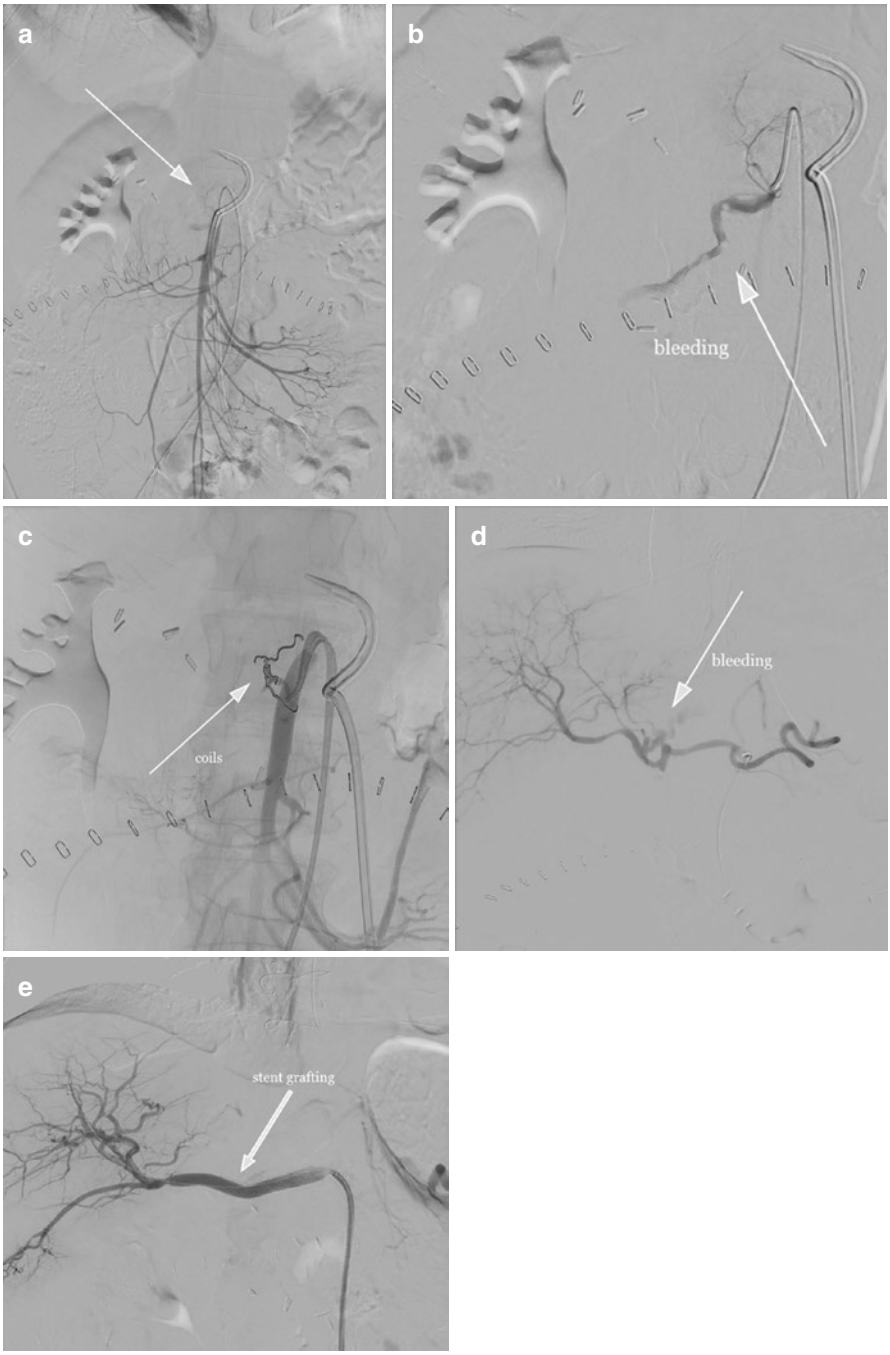

Fig. 67.4 (**a**, **b**) Active bleeding from a branch of the superior mesenteric artery, (**c**) successful coiling with angiography, (**d**) active bleeding from the hepatic artery, (**e**) stent grafting of the hepatic artery with preservation of the blood flow to the liver

stable, at least an interventional percutaneous drainage of infected fluid collections should be performed for sepsis control after endovascular hemostasis.

It should be noted that some cases of late extraluminal bleeding with an anastomotic leak may clinically present as a gastrointestinal bleed. In such a case endoscopy can provide false positive findings and, thus, may delay adequate treatment [6, 10].

67.4 Discussion

After the ISGPS developed and published an objective definition and clinical grading in 2007 in order to introduce a guideline for appropriate management of PPH and to compare outcomes, several validation studies based on retrospective research were published [8, 20, 22, 23]. It can be stated that the ISGPS classification proves suitable for clinical as well as scientific application, for comparing management and outcome, and for identifying risk factors for PPH. There is comprehensive data for severe and delayed hemorrhage while the data situation for PPH Grade A is sparse. This is because clinically not significant, mild bleeding is often not captured in standard databases. However, a study on a large cohort of 2429 patients showed no differences in mortality, ICU stay and readmission rates comparing patients with PPH Grade A to a cohort without cases of bleeding. It can be concluded, that Grade A PPH has no relevant clinical impact and requires no intervention [30]. The most important factor for distinguishing different types of PPH is the time of onset due to different pathogenesis of bleeding and consequently different mortality rates. Early bleeding which accounts for 9%–36% of all PPH events has much better outcome then delayed bleeding with mortality rates of 1,2% and 10,6%, respectively [8, 20, 23, 31]. Late hemorrhage results in most cases from POPF and is accompanied by sepsis as an additional comorbidity, which may contribute to higher mortality rates [12]. Several studies published a significant correlation (up to 80%) of Grade B and C PPH and POPF [8, 30, 32, 33] as well as pseudoaneurysms [25, 34, 35]. Grützmann et al. reported that pancreatic fistula increased the mortality in the PPH cohort 17-fold [6].

Generally, there are two different pathways of management: re-laparotomy for early and interventional radiology for delayed bleeding events. Although some authors preferred immediate re-laparotomy in case of sentinel bleeding in the past, the endovascular approach is recommended as the first-choice therapy of delayed PPH nowadays [6, 11, 12]. Standop et al. reported that re-operation in case of complications after pancreatectomy is associated with a high mortality rate of 13–60% [36]. Thus, in current literature, there is a clear shift towards interventional radiology as a first-line treatment for delayed PPH [12, 13, 15, 32, 35]. However, endovascular therapy of PPH itself is associated with complications. Thus, several studies reported about morbidity, mortality, and long-term results after endovascular intervention (e.g. recurrent bleeding 7–30%, hepatic failure 12–63% and mortality 7–54%) [12, 13]. A meta-analysis of 15 studies and 248 patients with PPH

showed comparable success rates for hemostasis (76% vs. 80%; P = 0.35) and significantly lower mortality rates after endovascular intervention compared to surgery (22% vs. 47%; P = 0.02). A technical success rate of 82–100% has been reported for interventional radiology as a treatment for PPH [12, 13, 24]. Consequently, some authors recommend attempting resuscitation of hemodynamic stability even in critical cases to allow endovascular management first [25].

Correa-Gallego et al. reported low mortality of 3% for PPH if its promptly recognized and adequately managed [23]. This emphasizes the recommendations for centralization of pancreatic surgery in high volume centers, since failure to rescue rates are much lower in specialized centers [4, 37].

67.5 Conclusion

PPH is categorized in early and late, intra- and extraluminal, and mild and severe. In cases of massive hemorrhage, immediate transfer to angiography or re-laparotomy should be undertaken. Patients in hemodynamic stable condition should undergo imaging with CT angiography. In case of intraluminal bleeding an endoscopical intervention is indicated. In the very likely event of extraluminal bleeding, a pseudoaneurysm is the main cause of hemorrhage and patients should be first submitted to endovascular therapy. Surgical intervention for late hemorrhage carries a risk for new complications but is important for the control of sepsis.

PPH is a major complication after pancreatic surgery, which requires an adequate management. The outcome for postpancreatectomy bleeding seems to be better in high-volume centers.

References

1. Parikh P, Shiloach M, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Pitt HA. Pancreatectomy risk calculator: an ACS-NSQIP resource. HPB. 2010;12:488–97. https://doi.org/10.1111/j.1477-2574.2010.00216.x.
2. Distler M, Rückert F, Hunger M, Kersting S, Pilarsky C, Saeger HD, Grützmann R. Evaluation of survival in patients after pancreatic head resection for ductal adenocarcinoma. BMC Surg. 2013;13:12. https://doi.org/10.1186/1471-2482-13-12.
3. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006;244:10–5. https://doi.org/10.1097/01.sla.0000217673.04165.ea.
4. Krautz C, Nimptsch U, Weber GF, Mansky T, Grützmann R. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg. 2018;267:411–7.
5. Choi SH, Moon HJ, Heo JS, Joh JW, Kim Y II. Delayed hemorrhage after pancreaticoduodenectomy. J Am Coll Surg. 2004;199:186–91.
6. Yekebas EF, Wolfram L, Cataldegirmen G, et al. Postpancreatectomy hemorrhage: diagnosis and treatment—an analysis in 1669 consecutive pancreatic resections. Ann Surg. 2007;246:269–80.

7. Tien YW, Wu YM, Liu KL, Ho CM, Lee PH. Angiography is indicated for every sentinel bleed after pancreaticoduodenectomy. Ann Surg Oncol. 2008;15:1855–61.
8. Grützmann R, Rückert F, Hippe-Davies N, Distler M, Saeger HD. Evaluation of the international study Group of Pancreatic Surgery definition of post-pancreatectomy hemorrhage in a high-volume center. Surgery. 2012;151:612–20.
9. Kasumova GG, Eskander MF, Kent TS, Ng SC, Moser AJ, Ahmed M, Pleskow DK, Callery MP, Tseng JF. Hemorrhage after pancreaticoduodenectomy: does timing matter? HPB. 2016;18:861–9.
10. Floortje van Oosten A, Smits FJ, van den Heuvel DAF, van Santvoort HC, Molenaar IQ. Diagnosis and management of postpancreatectomy hemorrhage: a systematic review and meta-analysis. HPB. 2019;21:953–61.
11. Brodsky JT, Turnbull ADM. Arterial hemorrhage after pancreatoduodenectomy: the 'Sentinel Bleed.'. Arch Surg. 1991;126:1037–40. https://doi.org/10.1001/archsurg.1991.01410320127019.
12. Biondetti P, Fumarola EM, Ierardi AM, Carrafiello G. Bleeding complications after pancreatic surgery: interventional radiology management. Gland Surg. 2019;8:150–63.
13. Miura F, Asano T, Amano H, et al. Management of postoperative arterial hemorrhage after pancreato-biliary surgery according to the site of bleeding: re-laparotomy or interventional radiology. J Hepatobiliary Pancreat Surg. 2009;16:56–63.
14. Limongelli P, Khorsandi SE, Pai M, Jackson JE, Tait P, Tierris J, Habib NA, Williamson RCN, Jiao LR. Management of delayed postoperative hemorrhage after pancreaticoduodenectomy: a meta-analysis. Arch Surg. 2008;143:1001–7.
15. Wolk S, Grützmann R, Rahbari NN, Hoffmann RT, Plodeck V, Weitz J, Welsch T, Distler M. Management of clinically relevant postpancreatectomy hemorrhage (PPH) over two decades—a comparative study of 1 50 consecutive patients undergoing pancreatic resection. Pancreatology. 2017;17:943–50.
16. Reber PU, Baer HU, Patel AG, Wildi S, Triller J, Büchler MW. Superselective microcoil embolization: treatment of choice in high-risk patients with extrahepatic pseudoaneurysms of the hepatic arteries. J Am Coll Surg. 1998;186:325–30.
17. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH)–an international study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142:20–5.
18. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–8.
19. Bassi C, Marchegiani G, Dervenis C, Sarr M. Pancreas the 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2016;161:584–91.
20. Welsch T, Eisele H, Zschäbitz S, Hinz U, Büchler MW, Wente MN. Critical appraisal of the international study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreatoduodenectomy. Langenbecks Arch Surg. 2011;396:783–91.
21. Garcea G, Jackson B, Pattenden CJ, et al. Early warning scores predict outcome in acute pancreatitis. J Gastrointest Surg. 2006;10:1008–15.
22. Rajarathinam G, Kannan DG, Vimalraj V, Amudhan A, Rajendran S, Jyotibasu D, Balachandar TG, Jeswanth S, Ravichandran P, Surendran R. Post pancreaticoduodenectomy haemorrhage: outcome prediction based on new ISGPS clinical severity grading. HPB. 2008;10:363–70.
23. Correa-Gallego C, Brennan MF, D'Angelica MI, Dematteo RP, Fong Y, Kingham TP, Jarnagin WR, Allen PJ. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg. 2012;215:616–21.
24. Puppala S, Patel J, McPherson S, Nicholson A, Kessel D. Hemorrhagic complications after whipple surgery: imaging and radiologic intervention. Am J Roentgenol. 2011;196:192–7.
25. Schäfer M, Heinrich S, Pfammatter T, Clavien PA. Management of delayed major visceral arterial bleeding after pancreatic surgery. HPB. 2011;13:132–8.

26. Gaudon C, Soussan J, Louis G, Moutardier V, Gregoire E, Vidal V. Late postpancreatectomy hemorrhage: predictive factors of morbidity and mortality after percutaneous endovascular treatment. Diagn Interv Imaging. 2016;97:1071–7.
27. Rumstadt B, Schwab M, Korth P, Samman M, Trede M. Hemorrhage after pancreatoduodenectomy. Ann Surg. 1998;227:236–41.
28. Frattaroli FM, Casciani E, Spoletini D, Polettini E, Nunziale A, Bertini L, Vestri A, Gualdi G, Pappalardo G. Prospective study comparing multi-detector row ct and endoscopy in acute gastrointestinal bleeding. World J Surg. 2009;33:2209–17.
29. Eckardt AJ, Klein F, Adler A, Veltzke-Schlieker W, Warnick P, Bahra M, Wiedenmann B, Neuhaus P, Neumann K, Glanemann M. Management and outcomes of haemorrhage after pancreatogastrostomy versus pancreatojejunostomy. Br J Surg. 2011;98:1599–607.
30. Duarte Garcés AA, Andrianello S, Marchegiani G, Piccolo R, Secchettin E, Paiella S, Malleo G, Salvia R, Bassi C. Reappraisal of post-pancreatectomy hemorrhage (PPH) classifications: do we need to redefine grades a and B? HPB. 2018;20:702–7.
31. Wellner UF, Kulemann B, Lapshyn H, Hoeppner J, Sick O, Makowiec F, Bausch D, Hopt UT, Keck T. Postpancreatectomy hemorrhage-incidence, treatment, and risk factors in over 1,000 pancreatic resections. J Gastrointest Surg. 2014;18:464–75.
32. Chen Y-I, Yang JF, Friedland S, et al. Lumen apposing stents are superior to plastic stents in the management of pancreatic walled-off necrosis: a large international multicenter study. Gastrointest Endosc. 2017;85:AB470.
33. Jilesen APJ, Tol JAMG, Busch ORC, Van Delden OM, Van Gulik TM, Van Dijkum EJMN, Gouma DJ. Emergency management in patients with late hemorrhage after pancreatoduodenectomy for a periampullary tumor. World J Surg. 2014;38:2438–47.
34. Otah E, Cushin BJ, Rozenblit GN, Neff R, Otah KE, Cooperman AM. Visceral artery pseudoaneurysms following pancreatoduodenectomy. Arch Surg. 2002;137:55–9.
35. Asai K, Zaydfudim V, Truty M, Reid-Lombardo K, Kendrick M, Que F, Nagorney D, Andrews J, Farnell M. Management of a delayed post-pancreatoduodenectomy haemorrhage using endovascular techniques. HPB. 2015;17:902–8.
36. Blanc T, Cortes A, Goere D, Sibert A, Pessaux P, Belghiti J, Sauvanet A. Hemorrhage after pancreaticoduodenectomy: when is surgery still indicated? Am J Surg. 2007;194:3–9.
37. Hata T, Motoi F, Ishida M, Naitoh T, Katayose Y, Egawa S, Unno M. Effect of hospital volume on surgical outcomes after pancreaticoduodenectomy: a systematic review and meta-analysis. Ann Surg. 2016;263:664–72.

Chapter 68
Post-Operative Pancreatic Fistula After Pancreatic Surgery

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Take Home Messages

- Post-operative pancreatic fistula (POPF) is a serious complication and a major cause of morbidity and mortality in pancreatic surgery.
- POPF is graded into biochemical leaks, and grades B and C with clinical relevance.
- POPF occurs in about 20% of patients undergoing pancreatoduodenectomy, but usually <2% are serious (grade C).
- POPF may occur in up to 30–40% of patients undergoing distal resections, but usually have a less severe clinical course.
- Management consists of drainage (prolonged), ± total parenteral nutrition, and sometimes completion pancreatectomy in the critically ill patient.

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Pearls and Pitfalls
- Several risk factors exist and several risk scores have been proposed but few validated.
- The large variations in anastomotic techniques used likely reflects that none are superior in POPF mitigation.
- Use of prophylactic drains at time of surgery is controversial, with data pointing to both beneficial and detrimental effects on fistula rates.
- Use of ductal stents, in either head or distal resections, is not justified by existing data.
- Most prophylactic medical interventions have not been substantiated over time.
- Completion pancreatectomy may be required as a rescue procedure in severe leaks.

Future Perspectives
- The current understanding of POPF pathogenesis is incomplete.
- Better and larger trials of existing drugs to modify risk are needed.
- Botox injection in Sphincter of Oddi has proven beneficial in distal resections, but awaits result from randomized trials.
- The inflammasome, including pancreatitis, needs better understanding to prevent or treat POPF.
- The microbiome as a potential causative or contributory factor has emerged and needs further investigation.
- If, substantiated, antibiotics may gain an extended role in preventing POPF.

68.1 Introduction

Post-operative morbidity remains a challenge after pancreatic surgery. The complication of most concern is the development of a post-operative pancreatic fistula (POPF) [1]. The occurrence of a pancreatic leak leads to risk of infection, risk of bleeding and life-threatening sepsis with prolonged hospitalization, increased morbidity and increased risk of mortality. Understanding the cause, identifying modifiable risk factors and implementing preventive measures has been a focus of significant research by those with an interest in pancreatic surgery.

Severe POPF (Fig. 68.1) may be responsible for about one third of all deaths after pancreatic surgery and even though such fistulae occur in a relatively small proportion of patients (<2%), their impact on outcome is considerable [2]. Extrapolating from volume-outcome series, it is probable that some POPF may be avoided by meticulous attention to technique and perioperative management [3], yet the rate of about 15–17% CR-POPF (grades B and C) and <2% severe (grade C) fistulas across time-series and center-volumes is consistent. Studies from Sweden and Finland did not report a change in POPF rates after centralization of pancreatic surgery [4, 5], neither was cost nor length of stay associated with reduced POPF rates. Thus, factors other than volume and experience are likely to contribute to CR-POPF.

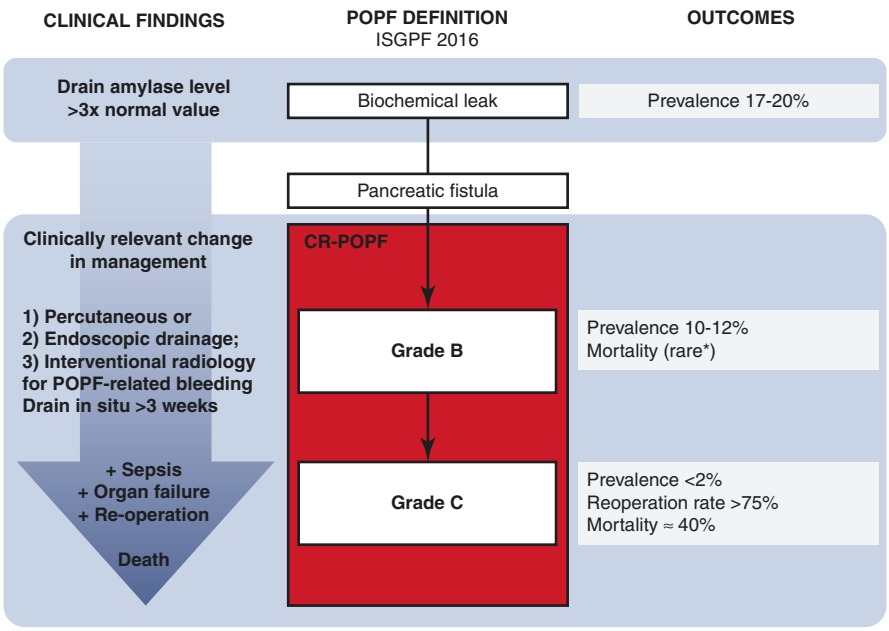

Fig. 68.1 Definition of POPF according to the 2016 ISGPS. Diagram based on the 2016 ISGPF definition. (*) Asterisk to indicate that any mortality related to grade B POPF is to be graded as type C, per definition. Only very rarely is a sudden post-operative death event in the presence of a POPF grade B truly unrelated to the fistula. POPF denotes post-operative pancreatic fistula. CR-POPF denotes "clinically relevant- POPF". (Reproduced with permission from Soreide K et al. HPB 2019 Dec;21(12):1621–1631, ©2019 with permission from Elsevier)

68.2 Definition of POPF

Until 2005, no uniform definition of pancreatic leaks existed. A 2005 consensus report initially standardized reporting of the incidence and outcome of POPF [6]. However, due to inconsistencies (in particular to grade A) further refinement took place with an updated definition in 2016 [7]. The new definition does not consider a biochemical leak (previously grade A) as a clinically relevant POPF (grade B and C; Fig. 68.1).

68.3 Risk Factors and Risk Scores of POPF

A better understanding of the underlying pathophysiology is crucial in order to better prevent and predict the occurrence of POPF [1]. The development of a POPF may be influenced by several concurrently occurring factors (Fig. 68.2) and the pathophysiological effects and interactions of each on the other are complex and poorly investigated.

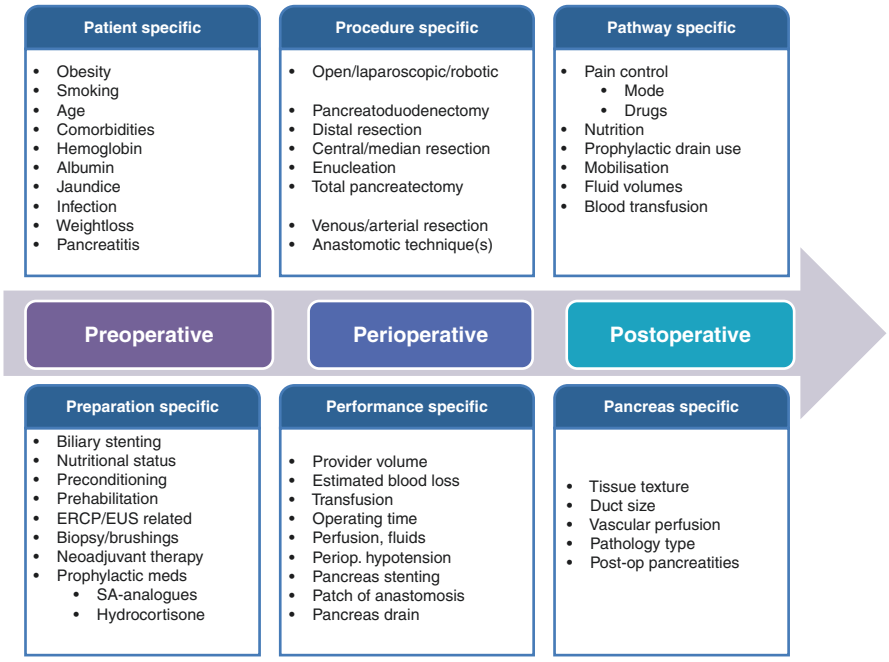

Fig. 68.2 Reported risk factors across the perioperative course in pancreatic surgery. The number of factors potentially influencing the POPF risk is depicted (list is not exhaustive but includes frequently debated factors). (Reproduced with permission and modifications from Soreide K et al. HPB 2019 Dec;21(12):1621–1631, ©2019 with permission from Elsevier)

68.3.1 Risk Scores for POPF

Several risk scores (at the time of writing at least 13) and nomograms have been proposed to predict POPF. The most highly validated risk score for fistula development is the Fistula Risk Score [8], constructed of pancreatic gland texture (soft gland has higher risk), pancreatic duct diameter (smaller has higher risk), type of pathology (higher risk in patients without pancreatic cancer or chronic pancreatitis) and perioperative blood loss (higher risk with increasing blood loss). Critique of the FRS is that it can only be estimated after surgery (when blood loss is estimated). Thus, suggestions of both an 'alternative FRS' [9] (a-FRS; consisting of pancreatic texture, duct diameter, BMI (higher BMI carries higher risk) and an 'updated alternative FRS' [10] (ua-FRS; adding male sex to the a-FRS, males have higher risk) have emerged; of which the latter (ua-FRS) is suggested to also be useful for minimally invasive pancreatic surgery. The occurrence of new scores and inconsistent variable validation of scores underline that the endpoint (e.g. POPF) is a 'moving target' influenced by several parameters not captured in one simple risk score. Most of the scores have a mediocre accuracy (Area Under the Curve [AUC] usually well below 0.8), and hence their clinical value is limited.

68.3.2 The Pancreatic Gland and Anastomotic Healing

Poor healing of the pancreatic anastomosis with subsequent leakage of pancreatic juice and enzymes into the abdomen may represent one source, but leaks can also occur from the pancreas parenchyma or from subsequent sequelae, i.e. a leak due to injury or trauma not directly related to the anastomosis, or inflammation (e.g. post-operative pancreatitis).

Abdominal fluid collections occur in one in every five patients undergoing pancreatic surgery [11], with two-thirds of collections being asymptomatic, and only half of collections eventually requiring percutaneous drainage. In the latter group, this is most often due to a pancreatic fistula [11]. Distinction of pathophysiological steps that separate a self-contained or drainable leak from a progressive, CR-POPF that progresses to sepsis, organ failure and potential death is currently not available (Fig. 68.3).

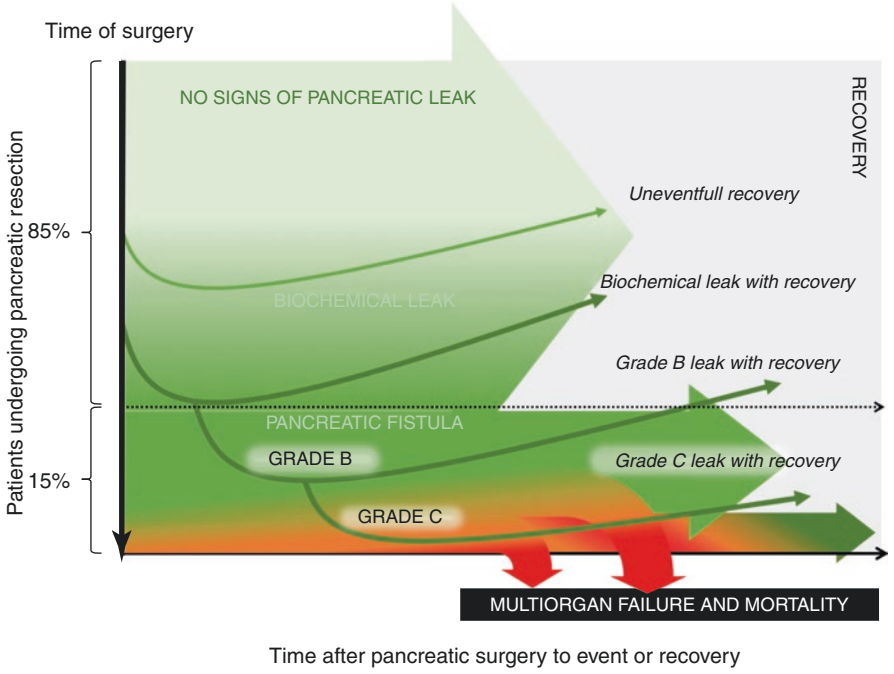

Fig. 68.3 The putative course of events of POPF after pancreatic surgery. Illustrated is examples with no leak, biochemical leak or a potential aggravation of leak into clinical relevant leak with recovery or, in some instances, progression to multiorgan failure and death. The likely sequence of events from surgical insult and potentially cascading events leading to severe POPF within the model is poorly understood, which is reflected in the vast number of factors investigated and the continued debate in the literature. Green colours resemble less harmful events with recovery, amber and red indicates progressive deranged physiology (e.g. organ failure and need for organ support), with risk of death. (Reproduced with permission from Soreide K et al. HPB 2019 Dec;21(12):1621–1631, ©2019 with permission from Elsevier)

68.3.3 Pancreatic Gland Texture

Glands containing more fibrosis (harder texture) have less risk of POPF. The pancreatic gland itself seems to be a crucial risk factor for POPF and is included in all of the most frequently used risk scores (FRS, a-FRS, and ua-FRS). However, considerable issues with standardization, robustness and validation exist with measurements derived from the gland itself.

The pancreatic parenchyma may be of variable quality and consistency with direct implication for development of POPF. While a 'soft' gland has a higher risk of POPF [12], there is no consensus in how to objectively score the gland texture [13]. A systematic review of gland texture confirmed the validity in risk between a 'firm' and 'soft' gland, yet stated the lack of an objective, reproducible and valid definition of this feature [13]. Administration of intraarterial octreotide did not result in any clinically relevant effect on tissue hardness [14].

Currently, the surgeon's tactile impression is what determines gland texture. This is problematic in that several scores include the distinction between 'soft' and 'firm', but there is no clear-cut definition or objective means by which to assess this [13]. The subjective and simple use of 'soft' and 'firm' is currently recommended. A histologic score based on fibrosis grade, fat content, pancreatic duct size, and signs of chronic pancreatitis was calculated in one study and correlated well with tissue hardness and suture holding capacity [15].

68.3.4 Pancreatic Duct Size

A small pancreatic duct ($\leq$3 mm) has been reported to be an independent risk factor for POPF [16, 17]. The combination of a soft gland and a small duct increases the risk for fistulae by several magnitudes [18]. No universal standard exist for measuring duct size (e.g. based on pre-operative imaging; intraoperatively, cut surface of gland, largest diameter etc).

68.3.5 Pancreatic Gland Perfusion

The neck of the pancreas is a 'watershed area' as a site of vascular anastomosis between the celiac and superior mesenteric arterial systems. Thus, hypoperfusion in this region may be associated with poor healing and risk of anastomotic breakdown. Intraoperative assessment of blood flow at the anastomotic site is frequently done by surgeons, but usually by inspection and palpation. In a prospective, non-randomized study [19], the blood supply at the cut surface of the pancreas was evaluated, and if found inadequate, the pancreas was cut back 1.5–2.0 cm to improve the blood supply. The technique resulted in a very low POPF rate of 1.6% [19].

In this regard, perioperative fluid balance may serve as a surrogate for adequate perfusion and, has been a matter of debate in relation to fluid type, volumes and measurements. Of note, patients with a higher net fluid balance 72 h after surgery have a higher rate of POPF [20, 21]. However, a systematic review found no definite difference with intraoperative fluid restriction and few studies on post-operative fluid restriction on POPF outcome [22]. Furthermore, a systematic review on use of "enhanced recovery" principles did not demonstrate any difference in POPF rate [23].

68.4 Multifactorial Pathogenesis and Sequence of Events

Risk factors related to POPF could be viewed as either ***modifiable*** (e.g. choice of anastomosis, use of drugs, stents, patches or drains) or ***non-modifiable*** (e.g. type of pathology, gender, age, obesity) [1, 24]. Further, there will be ***known risk factors*** (e.g. smoking, pre-operative biliary stenting) and ***unknown risk factors*** (e.g. type of microbiome, specific reaction to drugs and perioperative fluids, involvement of inflammasome and surgical stress) that are not specifically monitored for or measured in any individual patient [1]. Thus, a complete picture of all factors involved is not described in any one study nor any one single patient. Importantly, several of the factors that are described are related to each other, possibly confounding results and also interacting as modulators of progression and severity (Fig. 68.4).

68.4.1 Proteases from Pancreatic Juice

The pancreatic juice contains enzymes and proteases that may either digest the anastomosis or facilitate further leakage if disruption of the duct-to-mucosa anastomosis should occur. One report documented a possible indirect finding regarding the role of digestive enzymes with a lower POPF ratio when nonabsorbable (polyester) sutures were used compared to slow absorbable (polydioxanone) suture material in a propensity-score matched study [25]. A study using intraperitoneal microdialysis [26] to monitor intraperitoneal metabolites (glycerol, lactate, pyruvate and glucose) close to the pancreaticojejunostomy has shown that patients who later developed clinically significant POPF had higher intraperitoneal glycerol concentrations and lactate/pyruvate ratios, and lower glucose concentrations in combination with an increase in trypsinogen activation peptide. Also, several different measures of amylase in either serum or in drain fluids have been proposed to correlate with fistula risk. None of the findings are consistent or validated, but interest in pharmacological manipulation of factors involved in the microenvironment, inflammation and on the output of pancreatic juice have been taken on as a result of such findings.

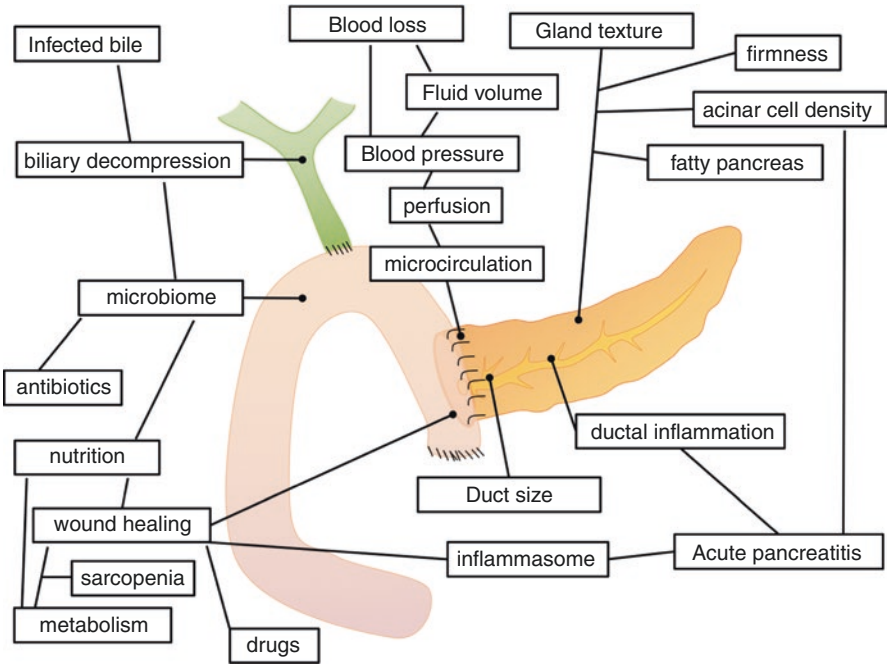

Fig. 68.4 Multifactorial pathogenesis and interaction of mechanisms in POPF. A number of factors investigated in relation to pancreatic fistula development. Contributions from metabolism, inflammasome and microbiome are suggested, as well as anatomic and disease specific contributions to risk. The model is not exhaustive but represent a conceptual framework for integrated research across disciplines. Contribution of the inflammasome and microbiome are poorly understood but likely are key players in the understanding of POPF development. (Reproduced with permission from Soreide K et al. HPB 2019 Dec;21(12):1621–1631, ©2019 with permission from Elsevier)

68.4.2 Inflammation and Post-Operative Pancreatitis

Post-operative pancreatitis is a clear risk factor for POPF [27], and this suggests that inflammation (even if sterile) may be an important contributor to POPF. One study found a correlation between pancreatic acinar cell density at the cut surface of the pancreas and the intraoperative amylase levels measured during surgery, to the subsequent frequency of pancreatitis and risk of POPF [28, 29]. Thus, a better understanding of the post-operative "inflammasome" may lead to new therapeutic targets and may provide new avenues for dampening the inflammatory signals that result from surgery in the immediate post-operative phase.

68.4.3 Microbiome in POPF

The understanding of the microbiome and its influence on outcome after pancreatic surgery is developing [30–32]. Bacterial contamination in ascitic fluid or intrabdominal contamination has been documented in association with POPF [33–37].

Likewise, contaminated bile, with or without pre-operative stenting, also increases the risk for POPF [38, 39]. Furthermore, it is documented that neoadjuvant therapy in PDAC is associated with different bacterial cultures in patients who undergo resection [31]. Sampling at multiple sites in patients undergoing pancreatoduodenectomy has revealed considerable changes in the microbiome, and patients with POPF had increased abundance of *Klebsiella* and decreased abundance of commensal anaerobes, such as *Ruminococcus*, in postoperative faecal samples [30].

Based on an increasing number of reports in the literature, it has become clear that the microbiome may influence surgical disease and outcomes in a range of ways not appreciated to date [40]. As the understanding of the bacterial load, species and interaction with human organ and tissues becomes clearer, we may learn more of their direct or indirect association with development of POPF.

68.5 Preventive Measures or Mitigation of Risk

With the associated risk in both pancreatoduodenectomy and distal resections, several strategies to mitigate this risk or even prevent POPF, have been tried, developed and incorporated (or, refuted) over the years. Roughly, one can separate these measures into those that are related to the surgery per se (type of resection and anastomotic techniques) and those that are part of the perioperative management.

68.5.1 Interventions to Reduce POPF After Distal Resections

The POPF rate after distal pancreatic resection is reported at around 30% across series [41, 42], with no difference between the open and laparoscopic approach. While usually not progressive to severe complications and death (e.g. grade C), POPF after distal pancreatectomy can contribute to morbidity, longer hospital stay and prolonged periods of drainage required for infection/output control.

A recent metanalysis of available techniques to reduce POPF after distal resection, found patch coverage after stapler or suture closure to have the lowest POPF rate and best outcomes among stump closure techniques after distal pancreatectomy [41], much in line with another metanalyses on the same topic [42].

The largest RCT on stapler versus hand-sewn closure of the pancreatic remnant after distal pancreatectomy (the DISPACT trial) found no difference between the two types of closure [43]. With the increasing use of laparoscopy for distal pancreatic resections [44, 45], but considerable variation in reported use and outcomes [46, 47], one may expect further trials to inform the optimal strategy. While some recommend and prefer reinforced stapler for laparoscopic distal resections, there is no documented benefit over regular staplers [42]. In a small, propensity score matched cohort, the use of reinforced stapler (12% POPF) was superior to transection with an ultrasonic dissector (40% POPF) [48], but considered hypothesis generating data at best. A Japanese RCT [49] found a non-significant difference comparing reinforced with regular staplers for distal resections (16.3% vs. 27.1%).

The transection site in distal pancreatectomy also seems to play a role in the development of POPF. Because of the normal anatomy, the pancreas is thinnest at its neck, ie over the portal vein, and is thicker towards the tail. Transection in the tail of the gland carries a higher risk of POPF compared with the neck [50], according to one study. However, deliberate transection at the neck might lead to unnecessary extra loss of pancreatic tissue which can contribute to the development of exocrine and endocrine pancreatic insufficiency.

Prophylactic pancreatic stenting has been proposed as a mitigation strategy for POPF in patients undergoing distal pancreatectomy. Although some series reported favorable results, the only randomized controlled trial carried out in Sweden, did not find any benefit of preoperative pancreatic stenting [51]. The results, although non-significant, actually suggested a harmful effect of stents in terms of POPF and infectious complications.

The use of pre-operative botulinum toxin injection in the sphincter of Oddi could provide a similar hypothetical benefit as pancreatic stenting (ie. free flow of pancreatic juice to the duodenum), possibly without the harm of stent placement. Botulinum has been demonstrated to reduce the POPF rate in a small phase I/II trial [52], but failed to be replicated in a single-center, retrospective series [53]. However, a multi-institutional trial is now underway in Germany (PREBOT trial).

68.5.2 Patches to Prevent Leaks in Pancreatoduodenectomy

Covering of the anastomosis with a sealant to protect from leakage is an intuitively attractive approach but evidence is weak with no or little effect, as reviewed elsewhere [1]. Several randomized trials and systematic reviews have failed to demonstrate any beneficial effect of Tachosil™ patches in reducing the risk of POPF [42, 54, 55].

Occlusion of the pancreatic duct with a chemical substance to avoid a pancreatic anastomosis during pancreaticoduodenectomy has been tried in a Dutch/Italian randomized clinical trial [56]. The trial found that duct occlusion (Ethibloc, Neoprene or Trasylol) without pancreaticojejunostomy did not reduce postoperative complications or mortality. However, the technique did significantly increase the risk of pancreatic endocrine insufficiency. A further trial [57] was recently performed using injection of a neoprene-based glue in the pancreatic duct for occlusion. In patients at high-risk of POPF, the POPF rate was reduced (to the level of a low-risk PJ anastomosis), but this technique almost tripled the risk of diabetes at 1 and 3 years after surgery.

68.5.3 Type of Anastomotic Reconstruction

Anastomosis of the pancreatic stump to the jejunum includes various forms such as end-to-side duct-to-mucosa anastomosis, and end-to-side or end-to-end invagination techniques (dunking). The most frequently used technique for pancreaticojejunostomy is the end-to-side, duct-to-mucosa anastomosis. However, it should be noted that

more than 66 variants of anastomotic techniques are reported in the literature [58], likely reflecting that none is superior to the other and that this is unlikely to be the solution to POPF.

Several meta-analyses (including a Cochrane review [59]) have investigated the effect of the two most commonly performed techniques (pancreaticogastrostomy and pancreaticojejunostomy) on fistula rates and found significantly different rates of POPF, in favor of pancreaticogastrostomy. The meta-analyses reported over the years have included different numbers of trials, with variable number of patients and also arrived at different conclusions due to the endpoints investigated other than POPF, such as biliary fistula rates and intra-abdominal fluid collections.

The superiority of pancreaticogastrostomy was reported in a recent meta-analysis, but only with slightly better results [60]. Furthermore, a small Canadian RCT found no difference between the two techniques, and the trial was stopped early [61]. Another negative trial found no long-term difference, but more post-operative bleeding events after pancreaticogastrostomy [62]. Based on results from surveys, almost 90% of surgeons use pancreaticojejunostomy in their current practice [63]. In another survey, more senior and experienced surgeons tended to use pancreaticogastrostomy [64]. Currently, the jury is still out on this, and practice seems to be based on institutional preferences.

68.5.4 Internal or External Stents

The use of stents, either internally or externally, to reduce POPF rates has also created debate over the years [65, 66]. Data remains conflicting, as one trial found a reduction in POPF by using external stents [66], while another trial found external stents were associated with a higher rate of POPF than internal stents [65]. In a large North-American multicenter study (n = 729 pancreatoduodenectomies), the use of external stents was placed at the surgeons' discretion (in about 18%) and found to be of value in risk-stratified patients who were at high risk of POPF [67]. Hence, weak data to support selective use of stents is available, however there is no support for routine use of this modality.

68.5.5 Placement of Intraperitoneal Drains After Surgery

The use of drains has caused considerable debate over the past few years, with arguments for and against their use [68]. Several meta-analyses have been undertaken with variable conclusions [69–73]. Routine use of drains is not supported by evidence, but still used by many, if not most, surgeons.

Concerns evolve around patients with a high-risk for development of POPF, and in this subgroup of patients drains may have a role (e.g. patients with a soft pancreas, small duct and high BMI), where the drains may give sentinel information about POPF development. The drain may thus help reduce failure-to-rescue rates.

Hence, the clinical practice is to place drains with a policy for early drain removal [74–78], if drain amylase is low (e.g. <1000 U/L) preferably by post-operative day 3 [79].

68.5.6 Perioperative Care to Mitigate POPF Rate

Several attempts at optimizing the perioperative care pathway by focusing on various types of care elements, interventions and preventive measures have been proposed over the years in order to prevent or reduce the impact of POPF. Risk scores are not universally used. Early detection parameters and selective use of various strategies is what is practiced in most centers, with accumulating data either being conflicting or not conclusive for one strategy over another.

Early detection of clinically relevant POPF is important. Variables associated with early diagnosis of POPF was identified in a systematic review and included [80]: non-serous drain efflux (day 3); positive drain culture (day 3); elevated temperature (any day); elevated C-Reactive Protein (CRP; day 4); elevated white blood cell count (day 4) and peripancreatic collections on computed tomography (CT; day 5–10).

68.5.7 Perioperative Drugs Associated with Risk of POPF

Use of non-opioid drugs after major gastrointestinal surgery has been promoted for enhanced-recovery and in enhanced recovery protocols. Use of non-steroidal anti-inflammatory drugs (NSAIDs) and the more specific cyclooxygenase-inhibitors (COX-2 inhibitors) have been linked to risk of anastomotic leaks in other gastrointestinal surgery. One study in patients undergoing pancreaticoduodenectomy found a non-significant increase in POPF rates with the use of NSAIDs (specifically the use of Ketorolac), and a significant increased risk of POPF for COX-2 inhibitors when adjusting for cofactors [81]. More recently, Ketorolac was proposed to increase the risk of POPF [82]. While data are still equivocal regarding the relationship of drugs to POPF, clinicians should be aware of a potential association to impaired wound healing if considering use in a fast-track/enhanced recovery setting where the focus is often on alternative pain medication to replace opioids after surgery.

68.5.8 Perioperative Use of Corticosteroids

Hydrocortisone has been demonstrated in two small trials to be effective in reducing overall postoperative complications after pancreatoduodenectomy [83] and POPF after distal pancreatectomy [84]. However, in an RCT comparing hydrocortisone to

a somatostatin-analogue, pasireotide, in patients with high-risk of POPF, hydrocortisone was not non-inferior to pasireotide, and pasireotide was more effective in preventing POPF after distal pancreatectomy [85]. Intraoperative dexamethasone was associated with reduced number of infectious complications in an observational cohort study [86], but no difference in major complications at 30 days was observed between the groups.

68.5.9 Preventive Use of Somatostatin-Analogues

Use of somatostatin and the somatostatin-analogues (octreotide, pasireotide, vapreotide, or lanreotide) to prevent POPF after pancreatic surgery remains a controversial and much debated topic. In a Cochrane review of 21 trials with a total of 2348 patients, there was a reduction in overall fistula rates with the use of somatostatin-analogues after pancreas surgery (RR 0.66; 95%CI 0.55–0.79). However, when investigating those trials that specifically reported clinically relevant fistula (CR-POPF), no difference was found (RR 0.69; 95%CI 0.38–1.28). Of note, most studies have been performed before the most recent revision of the POPF definition, hence a large number of POPFs may be simple biochemical leaks.

Two recent meta-analysis have investigated the effect of somatostatin-analogues and adds to the layer of confusion as they arrived at rather different conclusions [87, 88].

The first meta-analysis [87] (Fig. 68.5) included all studies, regardless of type of resection, somatostatin-analogues given and year of study. Including 15 studies of overall 2221 patients, they found statistically significant lower overall fistula rate and CR-POPF in the pooled analyses. However, as demonstrated in the figures, the study on pasireotide from Allen et al. [89] was a strong contributor to the pooled risk, and as the authors acknowledged, the heterogeneity between studies was considerable.

A further meta-analysis [88] (Fig. 68.6) including all RCTs investigating somatostatin-analogues after pancreatoduodenectomy, found 12 trials with a total of 1615 patients. The investigators found no difference in POPF. The overall POPF rate in the studies was 19.8% [88], with a pooled rate of 17.4% for SA-analogue and 22.3% for controls, for a non-significant difference between groups with a pooled odds ratio (OR) of 0.73 [95% CI 0.51–1.05; p = 0.09] . When looking only at the 6 trials that were reported after the 2005 POPF definition, there were no difference between groups. Finally, when exploring specifically for CR-POPF only, no difference with the use of prophylactic octreotide was identified. Furthermore, no difference was found in any other complications, including delayed gastric emptying, abdominal collections, reoperation, hospital stay nor in mortality [88].

Pasireotide is a relative new somatostatin-analogue used in the treatment of Cushing syndrome with a 40-times higher affinity to the somatostatin-5 receptor compared to other somatostatin-analogues. An RCT on pasireotide [89] demonstrated a significant reduction in clinically relevant fistulas, leaks and abscesses. The

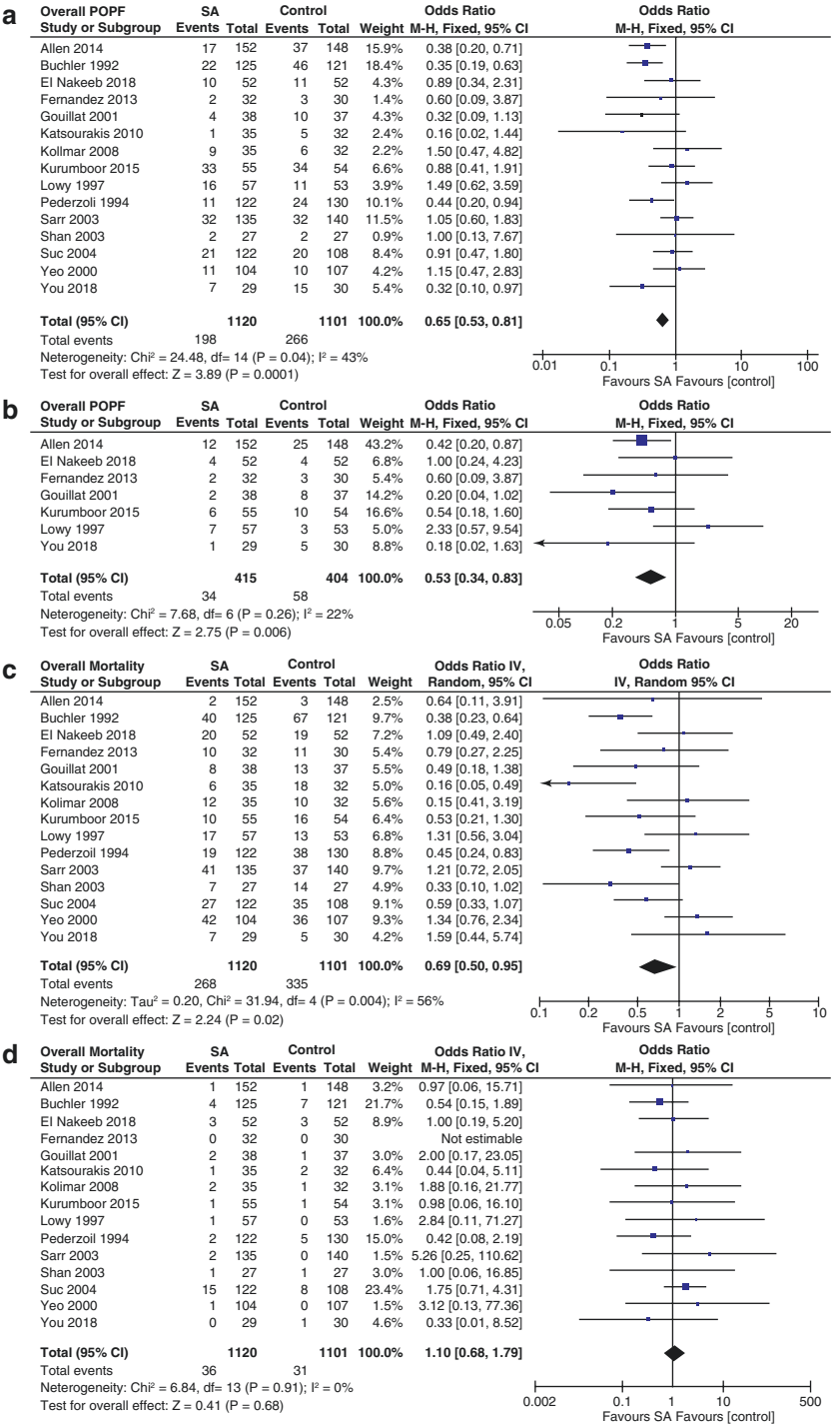

Fig. 68.5 Meta-analysis of somatostatin-analogues on outcomes after all types of pancreatic resections. Presented are the effect on (**a**) overall fistula rate, (**b**) clinical-relevant fistulae; (**c**) overall morbidity and (**d**) overall mortality. (Reproduced from on Tianpei et al., Pancreatology ©2019, with permission from Elsevier)

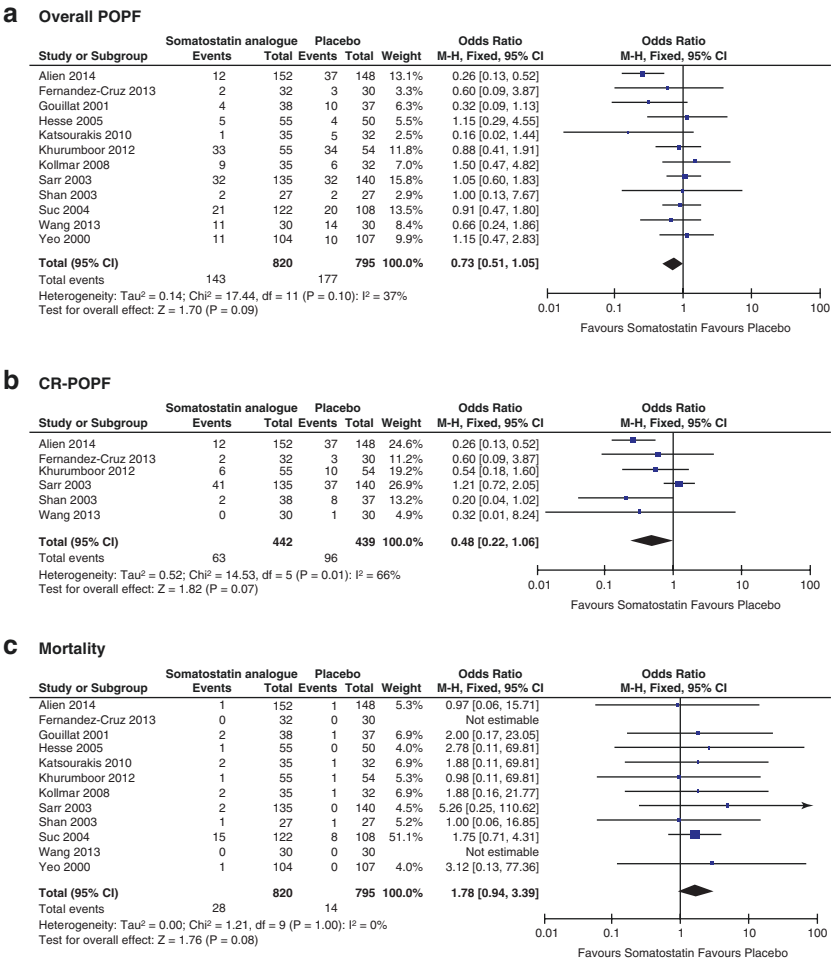

Fig. 68.6 Meta-analysis of somatostatin-analogues in RCTs after pancreatoduodenectomy. Effect of SA-analogue on (**a**) overall fistula rates (**b**) CR-POPF rates and (**c**) mortality, showing no effect for either of the subgroups. (Reproduced from Adiamah A, Arif Z, Berti F, et al. The Use of Prophylactic Somatostatin Therapy Following Pancreaticoduodenectomy: A Meta-analysis of Randomised Controlled Trials. World J Surg 2019;43:1788–1801, pending permission from Springer)

effect remained significant in favor of pasireotide when looking specifically at type of surgery (pancreaticoduodenectomy versus distal pancreatic resections) and duct size (dilated versus normal). However, the trial has since been heavily criticized for several reasons; a) using an institution-specific definition of POPF rather than using the ISGPF definition; b) having a slightly higher POPF rate (at around 20%) in the placebo group compared to other [90] series, and, c) lacking external validity as the trial was done in one center only. One Finnish RCT [85] found beneficial effect of pasireotide on POPF in distal pancreatic resections, compared to hydrocortisone. Others have not been able to replicate the findings in non-randomized studies,

reporting no effect on any of the outcomes [91]. Furthermore, pasireotide is more costly than other somatostatin-analogues, for which cost-effectiveness has not been demonstrated [92].

68.5.10 Antibiotics: From Prophylaxis to Perioperative Treatment?

With several reports on positive bile cultures, the use of biliary stenting (more so in the neoadjuvant setting) and the putative role of the microbiome in POPF, proposals for different ways of antibiotic management have developed [32, 37, 93]. However, in a recent RCT [94], the use of intraperitoneal irrigation of antibiotics did not reduce the number of surgical site infections, nor was there a reduced rate of CR-POPF in the two groups (11 versus 12%). Retrospective studies have not provided data to favor implementation of extended treatment of broad-spectrum antibiotics [93], and further research is needed to investigate the clinical impact of the microbiome and how this should be best handled.

68.6 Treatment of POPF

When a POPF is established by the definition (Fig. 68.1) it is important to tailor the intervention to avoid deterioration and progression to a severe type grade C POPF (Fig. 68.3).

68.6.1 Drains

For most clinically relevant POPF, simple drain placement (or, keeping an already intraoperatively placed drain) for a prolonged period may suffice. Patients with infectious signs, with or without positive bacterial cultures from bile (pre-stented bile duct) or in drain fluid, associated with fever, leukocytosis and increased CRP may warrant empirical administration of intravenous antibiotics pending results from cultures.

In severe POPF, catheter-based drainage as a "step-up-approach" has been suggested to be beneficial in management of severe POPF over direct relaparotomy [95, 96]. In a Dutch consecutive cohort, 309 (14.1%) patients developed severe POPF, with an in-hospital mortality of 17.8% (55 patients). Of these, 227 patients (73.5%) underwent primary catheter drainage and 82 patients (26.5%) underwent primary relaparotomy. Primary catheter drainage was successful (that is, survival without relaparotomy) in 175 patients (77.1%). After propensity score matching, 64 patients who underwent primary relaparotomy were matched to 64 patients who underwent primary catheter drainage. Mortality was lower after catheter drainage (14.1% vs.

35.9%). The rate of new-onset single-organ failure (4.7% vs. 20.3) and new-onset multiple-organ failure (15.6% vs. 39.1%) were also lower after primary catheter drainage [95]. In this study, acknowledging the limitations of propensity scores for matching, primary catheter drainage was favorable compared to primary relaparotomy.

68.6.2 Octreotide (Somatostatin-Analogues)

Other than prophylactic use, somatostatin-analogues have also been used in the *treatment* of pancreatic fistulas. However, data supporting this tradition is scarce. One meta-analysis pooled evidence for the use of octreotide to promote closure of POPF from seven RCTs [97]. Only 102 patients had fistula from the pancreas, and pooling of closure rates showed no significant difference between patients treated with somatostatin analogues compared with controls, for an odds ratio of 1.52 (95%CI 0.88–2.61) [97]. Of further note, recent studies [98, 99] have not been able to demonstrate the effect of octreotide in reducing the pancreatic juice output.

68.6.3 Nutritional Support

In patients with severe POPF, many would recommend nil per mouth and start parenteral nutrition as part of the supportive process towards healing when a POPF has developed. While total parenteral nutrition may be warranted in patients who are under intensive care and unable to swallow, it may not be of value in patients who are able to eat independently. In a multicentre, non-inferiority randomized trial of oral or enteral feeding of patients with POPF after pancreatoduodenectomy, a total of 114 patients were included, and received either oral (n = 57) or enteral (n = 57) feeding [100]. In the intention-to-treat analysis, oral feeding was non-inferior to enteral feeding in terms of 30-day fistula closure rate (88% versus 89%, respectively). Compared with enteral feeding, oral feeding significantly reduced hospital costs and duration of stay. No significant differences were noted in the number of patients whose POPF evolved into grade B/C, or any other outcomes. Extrapolating from the summarized RCT data from regular post-operative nutritional intake after pancreatoduodenectomy [101], the results also suggest that oral intake is the route preferred, if tolerated and possible.

68.6.4 Completion (Total) Pancreatectomy

In severe leaks and in patients not responding to the step-up management above (e.g. drainage of collections, antibiotics etc) with new onset or worsening organ failure, the only treatment may sometimes be to do a completion pancreatectomy

[102] in order to take out the source of the ongoing pathology. The timing and role of this is still controversial, with different attitudes to perform this across various institutions [96] and reported high mortality. Some very high-risk procedures (e.g. involving arterial resection and reconstruction) are now done with a planned total (complete) pancreatectomy as part of the procedure [103], based on the very detrimental consequences should even a minor leak occur after surgery.

68.7 Conclusions

The risk for POPF remains largely unchanged with several risk factors for patients with pancreatic cancer who need either a pancreatoduodenectomy or a distal resection [1]. Known risk factors may be used to tailor monitoring and the post-operative course. Several interventions, techniques and strategies have been suggested to mitigate risk, but few are universally effective. Even if a complete understanding of the pathophysiology of POPF is not available, novel technology and big data may help predict POPF risk better and earlier. Current risk models are based on only a handful of variables. Early data on machine learning may show promise, at least in the objective interpretation and use of imaging-based data [104]. Novel ideas and investigations into the cause of POPF should be embraced in order to hopefully reduce or even eliminate this risk of pancreatic surgery.

References

1. Søreide K, Healey AJ, Mole DJ, Parks RW. Pre-, peri- and post-operative factors for the development of pancreatic fistula after pancreatic surgery. HPB (Oxford). 2019;21(12):1621–31. https://doi.org/10.1016/j.hpb.2019.06.004.
2. Pedrazzoli S. Pancreatoduodenectomy (PD) and postoperative pancreatic fistula (POPF): a systematic review and analysis of the POPF-related mortality rate in 60,739 patients retrieved from the English literature published between 1990 and 2015. Medicine. 2017;96(19):e6858. https://doi.org/10.1097/md.0000000000006858.
3. Ecker BL, McMillan MT, Maggino L, Vollmer CM Jr. Taking theory to practice: quality improvement for pancreaticoduodenectomy and development and integration of the fistula risk score. J Am Coll Surg. 2018;227:430–438.e1. https://doi.org/10.1016/j.jamcollsurg.2018.06.009.
4. Antila A, Ahola R, Sand J, Laukkarinen J. Management of postoperative complications may favour the centralization of distal pancreatectomies. Nationwide data on pancreatic distal resections in Finland 2012–2014. Pancreatology. 2019;19(1):26–30. https://doi.org/10.1016/j.pan.2018.11.012.
5. Williamsson C, Ansari D, Andersson R, Tingstedt B. Postoperative pancreatic fistula-impact on outcome, hospital cost and effects of centralization. HPB. 2017;19(5):436–42. https://doi.org/10.1016/j.hpb.2017.01.004.
6. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138(1):8–13. https://doi.org/10.1016/j.surg.2005.05.001.

7. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584–91. https://doi.org/10.1016/j.surg.2016.11.014.
8. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013;216(1):1–14. https://doi.org/10.1016/j.jamcollsurg.2012.09.002.
9. Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, et al. Alternative fistula risk score for pancreatoduodenectomy (a-FRS): design and international external validation. Ann Surg. 2017;269:937–43. https://doi.org/10.1097/sla.0000000000002620.
10. Mungroop TH, Klompmaker S, Wellner UF, Steyerberg EW, Coratti A, D'Hondt M, et al. Updated alternative fistula risk score (ua-FRS) to include minimally invasive pancreatoduodenectomy: pan-European validation. Ann Surg. 2019. Publish Ahead of Print.; https://doi.org/10.1097/sla.0000000000003234.
11. Sierzega M, Kulig P, Kolodziejczyk P, Kulig J. Natural history of intra-abdominal fluid collections following pancreatic surgery. J Gastrointest Surg. 2013;17(8):1406–13. https://doi.org/10.1007/s11605-013-2234-1.
12. Distler M, Kersting S, Ruckert F, Kross P, Saeger HD, Weitz J, et al. Chronic pancreatitis of the pancreatic remnant is an independent risk factor for pancreatic fistula after distal pancreatectomy. BMC Surg. 2014;14:54. https://doi.org/10.1186/1471-2482-14-54.
13. Eshmuminov D, Schneider MA, Tschuor C, Raptis DA, Kambakamba P, Muller X, et al. Systematic review and meta-analysis of postoperative pancreatic fistula rates using the updated 2016 international study group pancreatic fistula definition in patients undergoing pancreatic resection with soft and hard pancreatic texture. HPB. 2018;20:992–1003. https://doi.org/10.1016/j.hpb.2018.04.003.
14. Belyaev O, Polle C, Herzog T, Munding J, Chromik AM, Meurer K, et al. Effects of intra-arterial octreotide on pancreatic texture: a randomized controlled trial. Scand J Surg. 2013;102(3):164–70. https://doi.org/10.1177/1457496913490457.
15. Belyaev O, Rosenkranz S, Munding J, Herzog T, Chromik AM, Tannapfel A, et al. Quantitative assessment and determinants of suture-holding capacity of human pancreas. J Surg Res. 2013;184(2):807–12. https://doi.org/10.1016/j.jss.2013.04.017.
16. Liu QY, Zhang WZ, Xia HT, Leng JJ, Wan T, Liang B, et al. Analysis of risk factors for postoperative pancreatic fistula following pancreaticoduodenectomy. World J Gastroenterol. 2014;20(46):17491–7. https://doi.org/10.3748/wjg.v20.i46.17491.
17. Su AP, Zhang Y, Ke NW, Lu HM, Tian BL, Hu WM, et al. Triple-layer duct-to-mucosa pancreaticojejunostomy with resection of jejunal serosa decreased pancreatic fistula after pancreaticoduodenectomy. J Surg Res. 2014;186(1):184–91. https://doi.org/10.1016/j.jss.2013.08.029.
18. Ansorge C, Strommer L, Andren-Sandberg A, Lundell L, Herrington MK, Segersvard R. Structured intraoperative assessment of pancreatic gland characteristics in predicting complications after pancreaticoduodenectomy. Br J Surg. 2012;99(8):1076–82. https://doi.org/10.1002/bjs.8784.
19. Strasberg SM, Drebin JA, Mokadam NA, Green DW, Jones KL, Ehlers JP, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg. 2002;194(6):746–58; discussion 59–60.
20. Winer LK, Dhar VK, Wima K, Lee TC, Morris MC, Shah SA, et al. Perioperative net fluid balance predicts pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg. 2018;22:1743–51. https://doi.org/10.1007/s11605-018-3813-y.
21. Wang S, Wang X, Dai H, Han J, Li N, Li J. The effect of intraoperative fluid volume administration on pancreatic fistulas after pancreaticoduodenectomy. J Invest Surg. 2014;27(2):88–94. https://doi.org/10.3109/08941939.2013.839766.
22. Chen BP, Chen M, Bennett S, Lemon K, Bertens KA, Balaa FK, et al. Systematic review and meta-analysis of restrictive perioperative fluid management in pancreaticoduodenectomy. World J Surg. 2018;42:2938–50. https://doi.org/10.1007/s00268-018-4545-6.

23. Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH. Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on pancreaticoduodenectomies. World J Surg. 2013;37(8):1909–18. https://doi.org/10.1007/s00268-013-2044-3.
24. Søreide K, Labori KJ. Risk factors and preventive strategies for post-operative pancreatic fistula after pancreatic surgery: a comprehensive review. Scand J Gastroenterol. 2016;51(10):1147–54. https://doi.org/10.3109/00365521.2016.1169317.
25. Andrianello S, Marchegiani G, Malleo G, Allegrini V, Pulvirenti A, Giardino A, et al. Polyester sutures for pancreaticojejunostomy protect against postoperative pancreatic fistula: a case-control, risk-adjusted analysis. HPB. 2018;20(10):977–83. https://doi.org/10.1016/j.hpb.2018.04.007.
26. Ansorge C, Regner S, Segersvard R, Strommer L. Early intraperitoneal metabolic changes and protease activation as indicators of pancreatic fistula after pancreaticoduodenectomy. Br J Surg. 2012;99(1):104–11. https://doi.org/10.1002/bjs.7730.
27. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. HPB. 2016;18(8):642–51. https://doi.org/10.1016/j.hpb.2016.05.006.
28. Nahm CB, Brown KM, Townend PJ, Colvin E, Howell VM, Gill AJ, et al. Acinar cell density at the pancreatic resection margin is associated with post-pancreatectomy pancreatitis and the development of postoperative pancreatic fistula. HPB. 2018;20(5):432–40. https://doi.org/10.1016/j.hpb.2017.11.003.
29. Laaninen M, Blauer M, Vasama K, Jin H, Raty S, Sand J, et al. The risk for immediate postoperative complications after pancreaticoduodenectomy is increased by high frequency of acinar cells and decreased by prevalent fibrosis of the cut edge of pancreas. Pancreas. 2012;41(6):957–61. https://doi.org/10.1097/MPA.0b013e3182480b81.
30. Rogers MB, Aveson V, Firek B, Yeh A, Brooks B, Brower-Sinning R, et al. Disturbances of the perioperative microbiome across multiple body sites in patients undergoing Pancreaticoduodenectomy. Pancreas. 2017;46(2):260–7. https://doi.org/10.1097/mpa.0000000000000726.
31. Goel N, Nadler A, Reddy S, Hoffman JP, Pitt HA. Biliary microbiome in pancreatic cancer: alterations with neoadjuvant therapy. HPB (Oxford). 2019;21(12):1753–60. https://doi.org/10.1016/j.hpb.2019.04.005.
32. Mussle B, Hempel S, Kahlert C, Distler M, Weitz J, Welsch T. Prognostic impact of Bacterobilia on morbidity and postoperative management after pancreatoduodenectomy: a systematic review and meta-analysis. World J Surg. 2018;42(9):2951–62. https://doi.org/10.1007/s00268-018-4546-5.
33. Nagakawa Y, Matsudo T, Hijikata Y, Kikuchi S, Bunso K, Suzuki Y, et al. Bacterial contamination in ascitic fluid is associated with the development of clinically relevant pancreatic fistula after pancreatoduodenectomy. Pancreas. 2013;42(4):701–6. https://doi.org/10.1097/MPA.0b013e31826d3a41.
34. Sugiura T, Mizuno T, Okamura Y, Ito T, Yamamoto Y, Kawamura I, et al. Impact of bacterial contamination of the abdominal cavity during pancreaticoduodenectomy on surgical-site infection. Br J Surg. 2015;102(12):1561–6. https://doi.org/10.1002/bjs.9899.
35. Morimoto M, Honjo S, Sakamoto T, Yagyu T, Uchinaka E, Amisaki M, et al. Bacterial smear test of drainage fluid after pancreaticoduodenectomy can predict postoperative pancreatic fistula. Pancreatology. 2019;19(2):274–9. https://doi.org/10.1016/j.pan.2019.01.018.
36. Maatman TK, Weber DJ, Qureshi B, Ceppa EP, Nakeeb A, Schmidt CM et al. Does the microbiology of Bactibilia drive postoperative complications after pancreatoduodenectomy? J Gastrointest Surg. 2019. https://doi.org/10.1007/s11605-019-04432-5.
37. Hata T, Mizuma M, Motoi F, Nakagawa K, Masuda K, Ishida M, et al. Early postoperative drainage fluid culture positivity from contaminated bile juice is predictive of pancreatic fistula after pancreaticoduodenectomy. Surg Today. 2019;50:248–57. https://doi.org/10.1007/s00595-019-01885-8.
38. Kajiwara T, Sakamoto Y, Morofuji N, Nara S, Esaki M, Shimada K, et al. An analysis of risk factors for pancreatic fistula after pancreaticoduodenectomy: clinical impact of bile juice

infection on day 1. Langenbecks Arch Surg. 2010;395(6):707–12. https://doi.org/10.1007/s00423-009-0547-z.
39. Fujii T, Yamada S, Suenaga M, Kanda M, Takami H, Sugimoto H, et al. Preoperative internal biliary drainage increases the risk of bile juice infection and pancreatic fistula after pancreatoduodenectomy: a prospective observational study. Pancreas. 2015;44(3):465–70. https://doi.org/10.1097/mpa.0000000000000265.
40. Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg. 2017;104(2):e14–23. https://doi.org/10.1002/bjs.10405.
41. Ratnayake CBB, Wells C, Hammond J, French JJ, Windsor JA, Pandanaboyana S. Network meta-analysis comparing techniques and outcomes of stump closure after distal pancreatectomy. Br J Surg. 2019;106(12):1580–9. https://doi.org/10.1002/bjs.11291.
42. Tieftrunk E, Demir IE, Schorn S, Sargut M, Scheufele F, Calavrezos L, et al. Pancreatic stump closure techniques and pancreatic fistula formation after distal pancreatectomy: meta-analysis and single-center experience. PLoS One. 2018;13(6):e0197553. https://doi.org/10.1371/journal.pone.0197553.
43. Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet. 2011;377(9776):1514–22. https://doi.org/10.1016/s0140-6736(11)60237-7.
44. Soreide K, Olsen F, Nymo LS, Kleive D, Lassen K. A nationwide cohort study of resection rates and short-term outcomes in open and laparoscopic distal pancreatectomy. HPB (Oxford). 2019;21(6):669–78. https://doi.org/10.1016/j.hpb.2018.10.006.
45. Lof S, Moekotte AL, Al-Sarireh B, Ammori B, Aroori S, Durkin D, et al. Multicentre observational cohort study of implementation and outcomes of laparoscopic distal pancreatectomy. Br J Surg. 2019;106(12):1657–65. https://doi.org/10.1002/bjs.11292.
46. Soreide K, Nymo LS, Kleive D, Olsen F, Lassen K. Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system. Pancreatology. 2019;19(6):880–7. https://doi.org/10.1016/j.pan.2019.07.047.
47. Ellis RJ, Zhang LM, Ko CY, Cohen ME, Bentrem DJ, Bilimoria KY, et al. Variation in hospital utilization of minimally invasive distal pancreatectomy for localized pancreatic neoplasms. J Gastrointest Surg. 2019; https://doi.org/10.1007/s11605-019-04414-7.
48. Pulvirenti A, Landoni L, Borin A, De Pastena M, Fontana M, Pea A, et al. Reinforced stapler versus ultrasonic dissector for pancreatic transection and stump closure for distal pancreatectomy: a propensity matched analysis. Surgery. 2019;166(3):271–6. https://doi.org/10.1016/j.surg.2019.02.016.
49. Kondo N, Uemura K, Nakagawa N, Okada K, Kuroda S, Sudo T, et al. A multicenter, randomized, controlled trial comparing reinforced staplers with bare staplers during distal pancreatectomy (HiSCO-07 trial). Ann Surg Oncol. 2019;26(5):1519–27. https://doi.org/10.1245/s10434-019-07222-0.
50. Sell NM, Pucci MJ, Gabale S, Leiby BE, Rosato EL, Winter JM, et al. The influence of transection site on the development of pancreatic fistula in patients undergoing distal pancreatectomy: a review of 294 consecutive cases. Surgery. 2015;157(6):1080–7. https://doi.org/10.1016/j.surg.2015.01.014.
51. Frozanpor F, Lundell L, Segersvard R, Arnelo U. The effect of prophylactic transpapillary pancreatic stent insertion on clinically significant leak rate following distal pancreatectomy: results of a prospective controlled clinical trial. Ann Surg. 2012;255(6):1032–6. https://doi.org/10.1097/SLA.0b013e318251610f.
52. Hackert T, Klaiber U, Hinz U, Kehayova T, Probst P, Knebel P, et al. Sphincter of Oddi botulinum toxin injection to prevent pancreatic fistula after distal pancreatectomy. Surgery. 2017;161(5):1444–50. https://doi.org/10.1016/j.surg.2016.09.005.
53. Volk A, Distler M, Mussle B, Berning M, Hampe J, Bruckner S, et al. Reproducibility of preoperative endoscopic injection of botulinum toxin into the sphincter of Oddi to prevent postoperative pancreatic fistula. Innov Surg Sci. 2018;3(1):69–75. https://doi.org/10.1515/iss-2017-0040.

54. Kwon J, Shin SH, Lee S, Park G, Park Y, Lee SJ, et al. The effect of fibrinogen/thrombin-coated collagen patch (TachoSil((R))) application in pancreaticojejunostomy for prevention of pancreatic fistula after pancreaticoduodenectomy: a randomized clinical trial. World J Surg. 2019;43(12):3128–37. https://doi.org/10.1007/s00268-019-05172-y.
55. Schindl M, Fugger R, Gotzinger P, Langle F, Zitt M, Stattner S, et al. Randomized clinical trial of the effect of a fibrin sealant patch on pancreatic fistula formation after pancreatoduodenectomy. Br J Surg. 2018;105(7):811–9. https://doi.org/10.1002/bjs.10840.
56. Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G, et al. Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. Ann Surg. 2002;236(4):422–8; discussion 8. https://doi.org/10.1097/01.sla.0000029244.62872.97.
57. Mazzaferro V, Virdis M, Sposito C, Cotsoglou C, Droz Dit Busset M, Bongini M, et al. Permanent pancreatic duct occlusion with neoprene-based glue injection after pancreatoduodenectomy at high risk of pancreatic fistula: a prospective clinical study. Ann Surg. 2019;270(5):791–8. https://doi.org/10.1097/sla.0000000000003514.
58. Daamen LA, Smits FJ, Besselink MG, Busch OR, Borel Rinkes IH, van Santvoort HC, et al. A web-based overview, systematic review and meta-analysis of pancreatic anastomosis techniques following pancreatoduodenectomy. HPB. 2018;20:777–85. https://doi.org/10.1016/j.hpb.2018.03.003.
59. Cheng Y, Briarava M, Lai M, Wang X, Tu B, Cheng N, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy. Cochrane Database Syst Rev. 2017;9:Cd012257. https://doi.org/10.1002/14651858.CD012257.pub2.
60. Ricci C, Casadei R, Taffurelli G, Pacilio CA, Beltrami D, Minni F. Is pancreaticogastrostomy safer than pancreaticojejunostomy after pancreaticoduodenectomy? A meta-regression analysis of randomized clinical trials. Pancreatology. 2017;17(5):805–13. https://doi.org/10.1016/j.pan.2017.07.003.
61. Grendar J, Ouellet JF, Sutherland FR, Bathe OF, Ball CG, Dixon E. In search of the best reconstructive technique after pancreaticoduodenectomy: pancreaticojejunostomy versus pancreaticogastrostomy. Can J Surg. 2015;58(2):154–9. https://doi.org/10.1503/cjs.010014.
62. Keck T, Wellner UF, Bahra M, Klein F, Sick O, Niedergethmann M, et al. Pancreatogastrostomy versus pancreatojejunostomy for RECOnstruction after PANCreatoduodenectomy (RECOPANC, DRKS 00000767): perioperative and long-term results of a multicenter randomized controlled trial. Ann Surg. 2016;263(3):440–9. https://doi.org/10.1097/sla.0000000000001240.
63. McMillan MT, Malleo G, Bassi C, Sprys MH, Vollmer CM Jr. Defining the practice of pancreatoduodenectomy around the world. HPB. 2015;17(12):1145–54. https://doi.org/10.1111/hpb.12475.
64. Kennedy GT, McMillan MT, Maggino L, Sprys MH, Vollmer CM Jr. Surgical experience and the practice of pancreatoduodenectomy. Surgery. 2017;162(4):812–22. https://doi.org/10.1016/j.surg.2017.06.021.
65. Jang JY, Chang YR, Kim SW, Choi SH, Park SJ, Lee SE, et al. Randomized multicentre trial comparing external and internal pancreatic stenting during pancreaticoduodenectomy. Br J Surg. 2016;103(6):668–75. https://doi.org/10.1002/bjs.10160.
66. Motoi F, Egawa S, Rikiyama T, Katayose Y, Unno M. Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. Br J Surg. 2012;99(4):524–31. https://doi.org/10.1002/bjs.8654.
67. McMillan MT, Ecker BL, Behrman SW, Callery MP, Christein JD, Drebin JA, et al. Externalized stents for pancreatoduodenectomy provide value only in high-risk scenarios. J Gastrointest Surg. 2016;20(12):2052–62. https://doi.org/10.1007/s11605-016-3289-6.
68. Andersson R, Soreide K, Ansari D. The dilemma of drains after pancreatoduodenectomy: still an issue? Scand J Surg. 2019;1457496919866014:145749691986601. https://doi.org/10.1177/1457496919866014.

69. Lyu Y, Cheng Y, Wang B, Zhao S, Chen L. Peritoneal drainage or no drainage after pancreaticoduodenectomy and/or distal pancreatectomy: a meta-analysis and systematic review. Surg Endosc. 2019. https://doi.org/10.1007/s00464-019-07293-w.
70. Zhang W, He S, Cheng Y, Xia J, Lai M, Cheng N, et al. Prophylactic abdominal drainage for pancreatic surgery. Cochrane Database Syst Rev. 2018;6:Cd010583. https://doi.org/10.1002/14651858.CD010583.pub4.
71. Schorn S, Nitsche U, Demir IE, Scheufele F, Tieftrunk E, Schirren R, et al. The impact of surgically placed, intraperitoneal drainage on morbidity and mortality after pancreas resection- a systematic review & meta-analysis. Pancreatology. 2018;18(3):334–45. https://doi.org/10.1016/j.pan.2018.02.013.
72. Huttner FJ, Probst P, Knebel P, Strobel O, Hackert T, Ulrich A, et al. Meta-analysis of prophylactic abdominal drainage in pancreatic surgery. Br J Surg. 2017;104(6):660–8. https://doi.org/10.1002/bjs.10505.
73. Huan L, Fei Q, Lin H, Wan L, Li Y. Is peritoneal drainage essential after pancreatic surgery?: a meta-analysis and systematic review. Medicine (Baltimore). 2017;96(51):e9245. https://doi.org/10.1097/md.0000000000009245.
74. Xourafas D, Ejaz A, Tsung A, Dillhoff M, Pawlik TM, Cloyd JM. Validation of early drain removal after pancreatoduodenectomy based on modified fistula risk score stratification: a population-based assessment. HPB (Oxford). 2019;21(10):1303–11. https://doi.org/10.1016/j.hpb.2019.02.002.
75. Smith H, Balaa FK, Martel G, Abou Khalil J, Bertens KA. Standardization of early drain removal following pancreatic resection: proposal of the "Ottawa pancreatic drain algorithm". Patient Saf Surg. 2019;13:38. https://doi.org/10.1186/s13037-019-0219-z.
76. Seykora TF, Maggino L, Malleo G, Lee MK, Roses R, Salvia R, et al. Evolving the paradigm of early drain removal following pancreatoduodenectomy. J Gastrointest Surg. 2019;23(1):135–44. https://doi.org/10.1007/s11605-018-3959-7.
77. Newhook TE, Vega EA, Vreeland TJ, Prakash L, Dewhurst WL, Bruno ML, et al. Early postoperative drain fluid amylase in risk-stratified patients promotes tailored post-pancreatectomy drain management and potential for accelerated discharge. Surgery. 2019;167:442–7. https://doi.org/10.1016/j.surg.2019.09.015.
78. Kalita DJ, Yadav J, Kalita D, Nyuwi KT, Madhav S. Role of day 1 drain amylase in predicting post operative pancreatic fistula. Surgery. 2019;166(3):429. https://doi.org/10.1016/j.surg.2019.02.002.
79. Linnemann RJA, Patijn GA, van Rijssen LB, Besselink MG, Mungroop TH, de Hingh IH, et al. The role of abdominal drainage in pancreatic resection—a multicenter validation study for early drain removal. Pancreatology. 2019;19(6):888–96. https://doi.org/10.1016/j.pan.2019.07.041.
80. Smits FJ, Molenaar IQ, Besselink MG, Borel Rinkes IHM, van Eijck CHJ, Busch OR, et al. Early recognition of clinically relevant postoperative pancreatic fistula: a systematic review. HPB (Oxford). 2019;22:1–11. https://doi.org/10.1016/j.hpb.2019.07.005.
81. Behman R, Karanicolas PJ, Lemke M, Hanna SS, Coburn NG, Law CH, et al. The effect of early postoperative non-steroidal anti-inflammatory drugs on pancreatic fistula following Pancreaticoduodenectomy. J Gastrointest Surg. 2015;19(9):1632–9. https://doi.org/10.1007/s11605-015-2874-4.
82. Kowalsky SJ, Zenati MS, Steve J, Lee KK, Hogg ME, Zeh HJ 3rd, et al. Ketorolac use may increase risk of postoperative pancreatic fistula after pancreaticoduodenectomy. J Surg Res. 2018;221:43–8. https://doi.org/10.1016/j.jss.2017.08.006.
83. Laaninen M, Sand J, Nordback I, Vasama K, Laukkarinen J. Perioperative hydrocortisone reduces major complications after Pancreaticoduodenectomy: a randomized controlled trial. Ann Surg. 2016;264(5):696–702. https://doi.org/10.1097/sla.0000000000001883.
84. Antila A, Siiki A, Sand J, Laukkarinen J. Perioperative hydrocortisone treatment reduces postoperative pancreatic fistula rate after open distal pancreatectomy. A randomized

placebo-controlled trial. Pancreatology. 2019;19(5):786–92. https://doi.org/10.1016/j.pan.2019.05.457.
85. Tarvainen T, Sirén J, Kokkola A, Sallinen V. Effect of hydrocortisone vs pasireotide on pancreatic surgery complications in patients with high risk of pancreatic fistula—a randomized clinical trial. JAMA Surg. 2020;155(4):291–8.
86. Sandini M, Ruscic KJ, Ferrone CR, Warshaw AL, Qadan M, Eikermann M, et al. Intraoperative dexamethasone decreases infectious complications after pancreaticoduodenectomy and is associated with long-term survival in pancreatic Cancer. Ann Surg Oncol. 2018;25(13):4020–6. https://doi.org/10.1245/s10434-018-6827-5.
87. Tianpei L, D'Cruz RT, Yang LS, Shelat VG. Somatostatin analogues and the risk of postoperative pancreatic fistulas after pancreatic resection—a systematic review & meta-analysis. Pancreatology. 2019;20:158–68. https://doi.org/10.1016/j.pan.2019.12.015.
88. Adiamah A, Arif Z, Berti F, Singh S, Laskar N, Gomez D. The use of prophylactic somatostatin therapy following pancreaticoduodenectomy: a meta-analysis of randomised controlled trials. World J Surg. 2019;43(7):1788–801. https://doi.org/10.1007/s00268-019-04956-6.
89. Allen PJ, Gonen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014;370(21):2014–22. https://doi.org/10.1056/NEJMoa1313688.
90. McMillan MT, Soi S, Asbun HJ, Ball CG, Bassi C, Beane JD, et al. Risk-adjusted outcomes of clinically relevant pancreatic fistula following pancreatoduodenectomy: a model for performance evaluation. Ann Surg. 2016;264(2):344–52. https://doi.org/10.1097/sla.0000000000001537.
91. Young S, Sung ML, Lee JA, DiFronzo LA, O'Connor VV. Pasireotide is not effective in reducing the development of postoperative pancreatic fistula. HPB (Oxford). 2018;20(9):834–40. https://doi.org/10.1016/j.hpb.2018.03.007.
92. Anderson R, Dunki-Jacobs E, Burnett N, Scoggins C, McMasters K, Martin RC. A cost analysis of somatostatin use in the prevention of pancreatic fistula after pancreatectomy. World J Surg. 2014;38(8):2138–44. https://doi.org/10.1007/s00268-014-2512-4.
93. Degrandi O, Buscail E, Martellotto S, Gronnier C, Collet D, Adam JP, et al. Perioperative antibiotherapy should replace prophylactic antibiotics in patients undergoing pancreaticoduodenectomy preceded by preoperative biliary drainage. J Surg Oncol. 2019;120(4):639–45. https://doi.org/10.1002/jso.25622.
94. Maatman TK, Weber DJ, Timsina LR, Qureshi B, Ceppa EP, Nakeeb A, et al. Antibiotic irrigation during pancreatoduodenectomy to prevent infection and pancreatic fistula: a randomized controlled clinical trial. Surgery. 2019;166(4):469–75. https://doi.org/10.1016/j.surg.2019.05.053.
95. Smits FJ, van Santvoort HC, Besselink MG, Batenburg MCT, Slooff RAE, Boerma D, et al. Management of severe pancreatic fistula after pancreatoduodenectomy. JAMA Surg. 2017;152(6):540–8. https://doi.org/10.1001/jamasurg.2016.5708.
96. Rangelova E, Valente R, Del Chiaro M. "Step-up approach" for the treatment of postoperative severe pancreatic fistula: is it really possible and useful? JAMA Surg. 2017;152(6):548–9. https://doi.org/10.1001/jamasurg.2016.5710.
97. Gans SL, van Westreenen HL, Kiewiet JJ, Rauws EA, Gouma DJ, Boermeester MA. Systematic review and meta-analysis of somatostatin analogues for the treatment of pancreatic fistula. Br J Surg. 2012;99(6):754–60. https://doi.org/10.1002/bjs.8709.
98. You DD, Paik KY, Park IY, Yoo YK. Randomized controlled study of the effect of octreotide on pancreatic exocrine secretion and pancreatic fistula after pancreatoduodenectomy. Asian J Surg. 2019;42(2):458–63. https://doi.org/10.1016/j.asjsur.2018.08.006.
99. Fernandez-Cruz L, Jimenez Chavarria E, Taura P, Closa D, Boado MA, Ferrer J. Prospective randomized trial of the effect of octreotide on pancreatic juice output after pancreaticoduodenectomy in relation to histological diagnosis, duct size and leakage. HPB (Oxford). 2013;15(5):392–9. https://doi.org/10.1111/j.1477-2574.2012.00608.x.

100. Wu JM, Kuo TC, Chen HA, Wu CH, Lai SR, Yang CY, et al. Randomized trial of oral versus enteral feeding for patients with postoperative pancreatic fistula after pancreatoduodenectomy. Br J Surg. 2019;106(3):190–8. https://doi.org/10.1002/bjs.11087.
101. Adiamah A, Ranat R, Gomez D. Enteral versus parenteral nutrition following pancreaticoduodenectomy: a systematic review and meta-analysis. HPB (Oxford). 2019;21(7):793–801. https://doi.org/10.1016/j.hpb.2019.01.005.
102. Bressan AK, Wahba M, Dixon E, Ball CG. Completion pancreatectomy in the acute management of pancreatic fistula after pancreaticoduodenectomy: a systematic review and qualitative synthesis of the literature. HPB (Oxford). 2018;20(1):20–7. https://doi.org/10.1016/j.hpb.2017.08.036.
103. Del Chiaro M, Rangelova E, Halimi A, Ateeb Z, Scandavini C, Valente R, et al. Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer. HPB (Oxford). 2019;21(2):219–25. https://doi.org/10.1016/j.hpb.2018.07.017.
104. Kambakamba P, Mannil M, Herrera PE, Muller PC, Kuemmerli C, Linecker M, et al. The potential of machine learning to predict postoperative pancreatic fistula based on preoperative, non-contrast-enhanced CT: a proof-of-principle study. Surgery. 2019;167:448–54. https://doi.org/10.1016/j.surg.2019.09.019.

Chapter 69
Delayed Gastric Emptying After Pancreatic Surgery

Christian Macutkiewicz

Take Home Messages

- Delayed gastric emptying has an incidence of 14–30%.
- Risk factors associated with an increased incidence are sepsis, intra-abdominal collections, post-operative pancreatic fistula and respiratory complications.
- Pylorus-preserving pancreaticoduodenectomy and classical Whipples show no difference in delayed gastric emptying.
- Antecolic reconstruction is favoured over retrocolic reconstruction.
- Enteral or parenteral nutrition, together with metoclopramide and erythromycin has been shown to be beneficial.

Pearls and Pitfalls

- Early recognition and management of pancreatic fistula will reduce incidence of delayed gastric emptying.
- A Braun entero-enterostomy is associated with a decreased incidence and severity of delayed gastric emptying after pylorus-resecting pancreaticoduodenectomy and should be considered.
- Meticulous surgical technique to minimise pancreatic fistula is probably the most important surgical aspect rather than the actual anastomosis or reconstruction technique used.

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Future Perspectives

- Further research is needed into the role of pyloric ring resection during pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy (SSPPD). Both these techniques show promise but require a randomised clinical trial to confirm superiority.

69.1 Introduction

Despite the improvement in technique, anaesthesia, perioperative and postoperative care that has come with centralisation of pancreatic surgery, postoperative morbidity remains high and is in the order of 30–50% [1–4]. Delayed gastric emptying (DGE), although not immediately life-threatening, is a frequent complication of pancreaticoduodenectomy, accounting for 14–30% of patients post-operatively [3, 5–7]. Delayed gastric emptying, or gastroparesis occurs due to the impaired motor function of the stomach to empty its contents. It is characterised by a prolonged use of a nasogastric tube, delay in commencement of oral nutrition or a replacement of nasogastric tube after a period of vomiting and is a common cause of prolonged hospitalisation or readmission following pancreatic surgery [8, 9] and therefore costs.

69.2 Definition of Delayed Gastric Emptying

Many definitions of delayed gastric emptying have been reported in the literature and most of them are based on the time taken for postoperative removal of the nasogastric tube or resumption of oral diet. There have been considerable differences in the definitions used, and thus made comparison of results difficult due to the lack of a consistent definition. In 2007, the International Study Group of Pancreatic Surgery (ISGPS) issued a position statement and suggested a definition and grading system which standardised the reporting of delayed gastric emptying in the literature [10]. It represents the inability to progress to a standard diet by the end of the first postoperative week and includes prolonged nasogastric intubation of the patient. They suggested that the mild, moderate and severe forms of delayed gastric emptying can be classified into grades A, B and C depending on their clinical impact (Table 69.1).

Table 69.1 The ISGPS definition of delayed gastric emptying after pancreatic surgery [10]

DGE grade	Nasogastric tube required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD**3**	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

Grade A is characterised by a patient requiring a nasogastric tube (NGT) between post-operative days (POD) 4 and 7, there is reinsertion of the NGT if the patient had nausea and vomiting after POD 3 or if the patient is unable to tolerate a solid diet by POD 7 but is able to before POD 14.

Grade B is present if an NGT is required from POD 8–14, if there is reinsertion of the NGT after POD 7, or if the patient is unable to tolerate a solid diet by POD 14 but is able to eat and drink before POD 21.

Grade C is present if the patient is unable to remove the nasogastric tube, or it has to be replaced after POD 14, or if the patient is still unable to maintain oral nutrition by POD 21.

The ISGPS definition of delayed gastric emptying was validated in 2010 by the Pancreatic Surgery unit in Verona, Italy [11]. They analysed 260 consecutive pancreaticoduodenectomies for complications and found pancreatic fistula in 23.1% of patients and delayed gastric emptying in 13.8%. On univariate and multivariate analysis they also found that clinically relevant pancreatic fistula, biliary fistula, abdominal collections, sepsis and pulmonary complications were statistically significant factors associated with delayed gastric emptying [11]. This was also evaluated by the Heidelberg unit in Germany. They also found that factors independently influencing delayed gastric emptying were female sex, preoperative heart failure and associated major complications [12].

69.3 Risk Factors Associated with Delayed Gastric Emptying

The pathophysiology of delayed gastric emptying is not fully understood. Possible causes have been postulated to involve a decrease in the plasma motilin levels with duodenectomy [13–15], disruption of the vagal innervation to the antrum and pylorus, and localised ischaemia of the pylorus and proximal duodenum [16, 17], or the improper alignment after reconstruction. These are referred to as primary delayed gastric emptying and are not as common as secondary delayed gastric emptying, where a complication or risk factor can be identified such as postoperative pancreatic fistula or retrogastric collection [18].

69.3.1 Preoperative Factors and Delayed Gastric Emptying

While there have been many studies looking at operative and postoperative factors associated with delayed gastric emptying, very few studies have looked at preoperative factors. Sarcopenia is defined as a loss of skeletal muscle leading to decreased strength and general physical performance with impaired resilience to stress [19]. It is found in almost 80% of cancer patients and is associated with decreased survival and increased recurrence rates in numerous malignancies, but particularly with pancreatic adenocarcinoma [20]. Tankel et al. studied the effect of sarcopenia in patients undergoing pancreaticoduodenectomy. They found that patients suffering with sarcopenia were six times more likely to have delayed gastric emptying [21].

69.4 Surgical Factors and Delayed Gastric Emptying

69.4.1 Pylorus-Preserving Pancreaticoduodenectomy Versus Classic Whipple Procedure

Many surgical techniques have been studied to investigate the causes of delayed gastric emptying or possible ways to decrease its incidence. Pylorus-preserving pancreaticoduodenectomy (PPPD) was reintroduced in the late 1970s by Traverso and Longmire for chronic pancreatitis [22]. It was thought that preservation of the pylorus would lead to better gastrointestinal function, less dumping and improved postoperative weight gain [23]. However there were concerns over resection margins, and an increase in the complications rates, particularly with delayed gastric emptying [3].

Early studies showed increased rates of delayed gastric emptying after PPPD because of pylorospasm [24]. This led to numerous modifications such as pyloromyotomy, pyloric dilatation and pyloric resection [25–27]. In fact, Fischer and Hong performed their prospective study and confirmed a significant decrease in the incidence of delayed gastric emptying by performing a pyloric dilation prior to anastomosis [25], something that all four studies confirmed compared with PPPD alone.

Pyloric ring resection was introduced as an alternative to pyloric dilatation in which the pyloric ring and duodenum are resected, leaving the majority of the stomach intact to act as a reservoir for food. Fujii et al. compared the PPPD with the classical Whipple procedure, and subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) and found significant reduction in the incidence of delayed gastric emptying, with 27.3%, 5.8% and 5.4% respectively [28]. This was also confirmed by the Heidelberg unit in 2013. Hackert et al. studied 40 patients who underwent a pylorus-resecting pancreaticoduodenectomy and pair-matched the group with patients who underwent a PPPD. They found the incidence of delayed gastric emptying was significantly reduced in the pylorus-resecting group with an incidence of delayed gastric emptying of 15% compared with 42.5% [29]. Their incidence of delayed gastric emptying in the standard group with significantly higher than many other units however and a randomised clinical trial has yet to be performed to confirm a difference. A meta-analysis of pylorus-preserving versus pylorus-resecting pancreaticoduodenectomy involving 992 patients however found no difference in relation to delayed gastric emptying [30].

Tran et al. compared PPPD with the standard Whipple procedure and found no differences in delayed gastric emptying between the two techniques, with 22% and 23% incidence of delayed gastric emptying in both groups. They also found that there was no difference in length of stay, postoperative pancreatic fistula (13% vs. 14%) and found that delayed gastric emptying was associated with postoperative pancreatic fistula and sepsis [31].

The Heidelberg group performed a meta-analysis in which they analysed three randomised clinical trials and eight non-randomised studies with a total of 992

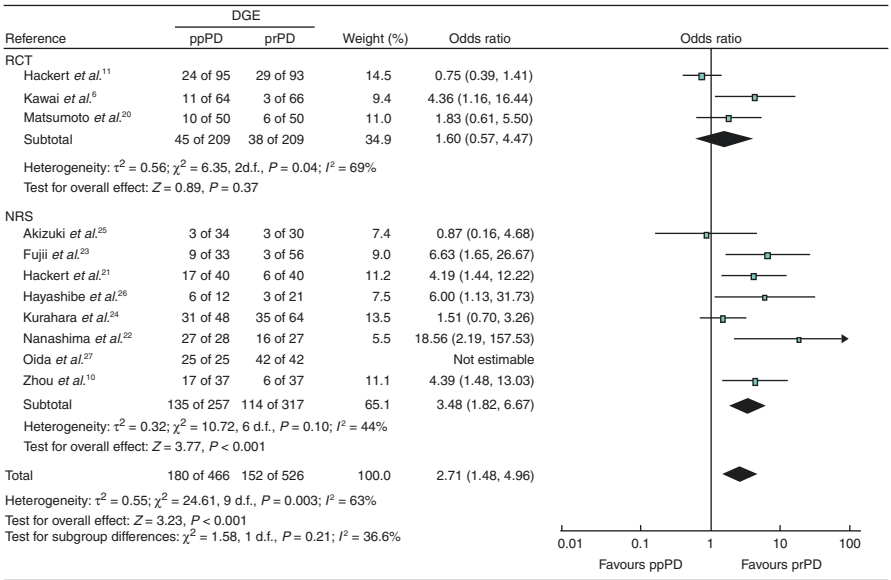

Fig. 69.1 Meta-analysis of pylorus-preserving compared to pylorus resecting pancreatoduodenectomy and the risk of DGE. *RCT* randomized controlled trial, *NRS* non-randomised studies. (Reproduced from Klaiber U, et al. Meta-analysis of delayed gastric emptying after pylorus-preserving versus pylorus-resecting pancreatoduodenectomy. Br J Surg. 2018;105 (4):339–349 with permission from Wiley)

patients [30]. In the analysis of all studies found that standard Whipple was superior regarding delayed gastric emptying and length of hospital stay, however there was substantial statistical heterogeneity in the studies (Fig. 69.1). In the subgroup analysis using only the randomised clinical trials there was no statistical difference between PPPD and standard Whipple with regard to delayed gastric emptying [30].

69.4.2 Billroth I Versus Billroth II Vs. Roux-en-Y Reconstruction

There is a theoretical advantage in utilising a Billroth I reconstruction post pancreaticoduodenectomy because the sequence of anastomoses is similar to the normal anatomy. However, all the three anastomoses lie in very close proximity due to the limitation of available space which could therefore impair gastric emptying. Billroth II and Roux-en-Y reconstructions, on the other hand, place the gastrojejunal anastomosis away from the pancreatic and biliary anastomoses. Therefore, theoretically, Billroth I reconstruction may increase the incidence of delayed gastric emptying.

Studies looking into Billroth I, Billroth II and Roux-en-Y construction found significantly higher rates of delayed gastric emptying with Billroth I reconstruction

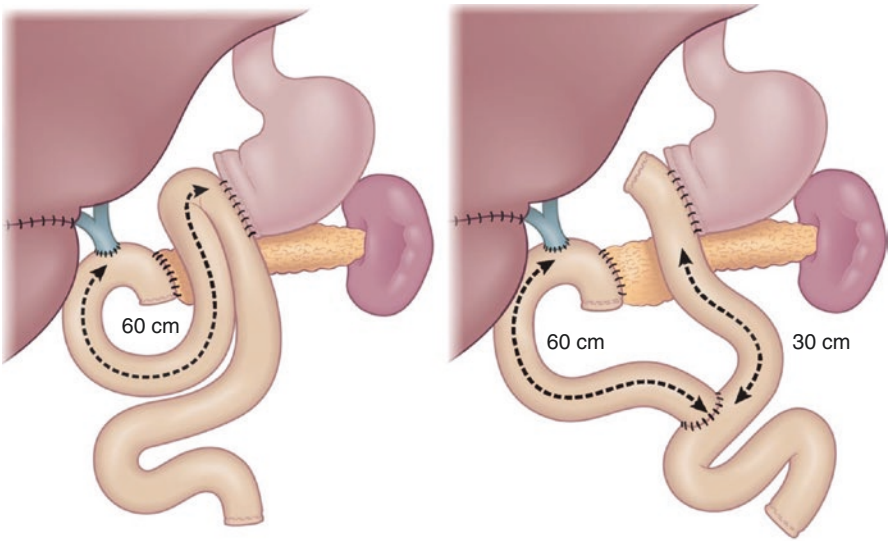

Fig. 69.2 Two types of gastrojejunostomy: Billroth II and Roux-en-Y reconstruction. Billroth II (left) and Roux-en-Y reconstruction (right). (Reproduced from Busquets J, et al. Randomized trial of two types of gastrojejunostomy after pancreatoduodenectomy and risk of delayed gastric emptying (PAUDA trial). Br J Surg. 2019;106 (1):46–54 with permission from Wiley)

as compared to Billroth II reconstruction and Roux-en-Y reconstruction [32]. Shimoda et al. performed a randomised clinical trial looking into the effect of Roux-en-Y reconstruction and found significantly higher rates of delayed gastric emptying with Roux-en-Y as compared to Billroth II reconstruction [33]. A further randomised clinical trial comparing Billroth II versus Roux-en-Y reconstruction (PAUDA trial) with 40 patients in each arm found no difference between the two techniques [34]. Therefore the published data suggests that Billroth II reconstruction may be associated with a lower incidence of delayed gastric emptying compared to Billroth I or Roux-en-Y reconstruction but the literature is heterogeneous and a strong recommendation for Billroth II or Roux-en-Y reconstruction cannot be made to reduce delayed gastric emptying (Fig. 69.2).

69.4.3 Antecolic Versus Retrocolic Reconstruction Following Pancreaticoduodenectomy

The antecolic route for reconstruction of the gastrojejunostomy has been preferred due to theoretical advantages that the anastomosis has the colon between the pancreatic anastomosis and the gastrojejunal anastomosis, thereby offering protection from any pancreatic fistula that may develop postoperatively. There is also less chance of angulation or kinking of the gastrojejunostomy without the mesocolon pressing on

the anastomosis or venous congestion of the jejunal loop used for reconstruction. Both retrospective studies and randomised clinical trials have compared the two reconstruction techniques and found either no difference, an advantage of antecolic reconstruction over retrocolic anastomosis or the opposite findings [35–39].

In 2015, Bell et al. performed a meta-analysis of 9 studies with a total of 878 patients comparing antecolic versus retrocolic reconstruction. They found that antecolic reconstruction was associated with a lower relative risk of delayed gastric emptying, a lower length of stay, and an earlier return to oral diet. They also found no difference in pancreatic fistula or mortality [40].

The largest meta-analysis included 7 randomised clinical trials and 8 retrospective studies comparing the incidence of delayed gastric emptying in 2270 patient [41]. The overall incidence of delayed gastric emptying was 27.2% and they found that the antecolic route of gastrojejunostomy showed a significantly lower incidence of delayed gastric emptying, length of stay and earlier commencement of oral nutrition when compared to retrocolic anastomosis [41].

69.4.4 Braun's Entero-Enterostomy

The reflux of bile into the stomach from the gastroenterostomy has been proposed as a possible cause of delayed gastric emptying [42]. To mitigate this in the setting of gastric surgery, an enteroenterostomy between afferent and efferent limbs of the gastroenterostomy was proposed by Braun over 100 years ago to divert bile from the afferent limb into the stomach.

The use of a Braun enteroenterostomy following a classic pancreaticoduodenectomy has therefore the potential to stabilise and reduce any kinking at the gastrojejunostomy. Food passing through either the afferent or efferent limbs can progress distally through the Braun enteroenterostomy. It also directs pancreatic and biliary secretions away from the stomach, thereby reducing the exposure of the gastric mucosa to the irritating effects of bile. It also protects from pressure increases in the biliopancreatic limb when there is oedema and kinking of the gastrojejunostomy.

There have been several retrospective studies comparing the rates of delayed gastric emptying with or without a Braun's enteroenterostomy [42–44]. These have shown a significant decrease in the incidence of delayed gastric emptying, with one study finding a delayed gastric emptying rate of 35% with standard reconstruction and only 4.2% with a Braun enteroenterostomy [43]. Fujieda et al. carried out a randomised clinical trial looking at the effect of a Braun enteroenterostomy on intragastric bile reflux and delayed gastric emptying. They found that the Braun enteroenterostomy did not reduce the intragastric bile reflux and had only a minor effect on delayed gastric emptying. The incidence of delayed gastric emptying was 29.4% in the non-Braun group and 20.6% in the Braun group, but this was not statistically significant [45]. Zhou et al. carried out a meta-analysis in 2018 involving 1672 patients in the hope that they could provide a definitive answer to the question. They found that a Braun enteroenterostomy not only reduced the incidence of

delayed gastric emptying but also its clinical severity [46]. The conclusion therefore is that after a pylorus-resecting pancreaticoduodenectomy, a Braun enteroenterostomy is probably associated with a decreased incidence and severity of delayed gastric emptying.

69.4.5 Pancreaticojejunostomy Versus Pancreaticogastrostomy

The effect of pancreatic anastomosis on delayed gastric emptying has been investigated by many units. There is a view that a pancreaticogastrostomy has a theoretical advantage because any pancreatic leak or collection will not contain activated pancreatic enzymes. However, delayed gastric emptying has been shown to be associated with intra-abdominal collections near the stomach and therefore if there are leaks from the pancreaticogastrostomy, then this may actually increase delayed gastric emptying [18]. Bassi et al. carried out a randomised clinical trial comparing pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) in 2005 [47]. They randomised 151 patients and found that delayed gastric emptying was associated in 3% of PG versus 12% of PJ patients. They did however find that PG patients who had delayed gastric emptying and a pancreatic fistula had a severe clinical impact.

In 2018, Lyu et al. carried out a meta-analysis of 7 randomised clinical trials with a total of 1184 patients. They found no difference in post-operative pancreatic fistula, delayed gastric emptying or mortality and morbidity. They did however find that pancreaticogastrostomy was associated with a slightly higher incidence of post-pancreatectomy haemorrhage and suggested that this could be reduced using a two-layer anastomosis [48].

69.5 Post-Operative Factors in Delayed Gastric Emptying

In every study looking at risk factors for delayed gastric emptying, the recurring post-operative factor associated with an increased incidence is post-operative pancreatic fistula [49–51]. In their original validation paper of the ISGPS classification of delayed gastric emptying, Malleo et al. analysed 260 consecutive patients undergoing pancreaticoduodenectomy. They found on univariate analysis that abdominal collections, clinically relevant pancreatic fistula, biliary fistulas, sepsis and pulmonary complications were all associated with delayed gastric emptying. On multivariate analysis, only clinically relevant pancreatic fistula and biliary fistulas were associated with delayed gastric emptying [11].

A similar finding was seen by the Karolinska unit in Sweden. They looked at 327 patients undergoing pancreatic resection and found that pancreatic fistula was the most significant factor associated with delayed gastric emptying [18]. Liu et al. analysed 196 consecutive pancreaticoduodenectomy patients and also found that only postoperative complications instead of operative methods were associated with

delayed gastric emptying. They found that independent risk factors for delayed gastric emptying were clinically relevant post-operative pancreatic fistula and intra-abdominal collections [52].

69.6 Management Strategies for Delayed Gastric Emptying

The definition by the ISGPS has been helpful in standardising the reporting of delayed gastric emptying, however there is no standardised management. Many units investigate delayed gastric emptying with a gastrograffin contrast swallow to confirm hold-up in the stomach or even a gastroscopy to confirm patency of the afferent and efferent limbs of the gastrojejunostomy [11].

69.6.1 Prokinetic Drugs

Prokinetic agents such a metoclopramide are routinely used in the first instance and has been shown to decrease delayed gastric emptying [53]. However, the use of erythromycin has been more extensively studied. Yeo et al. performed a randomised clinical trial on the use of erythromycin after pancreaticoduodenectomy. They administered 200 mg of intravenous erythromycin or 0.9% saline to 118 consecutive patients undergoing pancreaticoduodenectomy and found a 37% reduction in the incidence of delayed gastric emptying (19% vs. 30%) in the erythromycin patients [54].

69.6.2 Somatostatin

Somatostatin analogues are often routinely used following pancreaticoduodenectomy. Despite numerous randomised trials, no benefit in its routine use has been found to reduce either post-operative pancreatic fistula or delayed gastric emptying [55].

69.6.3 Nutrition

Patients with delayed gastric emptying are at high risk of malnutrition and therefore steps should be made to provide supplemental nutrition until the patient is able to sustain normal nutrition and delayed gastric emptying is no longer present. Optimal management of patients with delayed gastric emptying has been found to occur when supplementary nutrition is started within 10 days of the operation. Therefore

if Grade B or C delayed gastric emptying is suspected, then either total parenteral nutrition or jejunal feeding either via a nasojejunal feeding tube, or feeding jejunostomy should be considered [50].

69.6.4 Management of Related Complications

The majority of patients with delayed gastric emptying have a post-operative complication. Therefore, the of management of any complication that may be a contributory factor is paramount. Percutaneous drainage of any undrained collection, treating any pulmonary complications with chest physiotherapy and antibiotics, treating any diagnosed sepsis, and ensuring that there is no mechanical obstruction to the gastrojejunostomy are important steps in management.

Finally, studies looking at enhanced recovery for pancreatic surgery have found that complications, including delayed gastric emptying and respiratory complications can be reduced by adopting an enhanced recovery programme for pancreaticoduodenectomy patients such as early removal of nasogastric tube, early oral nutrition and mobilisation and physiotherapy [56–58].

69.7 Conclusion

Delayed gastric emptying is a common complication of pancreaticoduodenectomy affecting 14–30% of patients [4, 5, 54]. Risk factors associated with an increased incidence are sepsis, intra-abdominal collections, post-operative pancreatic fistula and respiratory complications. Management of these complications is imperative if delayed gastric emptying is to be treated successfully.

Meticulous surgical technique is important to try to reduce any post-operative complication and therefore any possibility of delayed gastric emptying. Pylorus-preserving pancreaticoduodenectomy or classic Whipple has no difference in the incidence of delayed gastric emptying. Antecolic reconstruction is superior to retrocolic reconstruction in reducing the incidence of delayed gastric emptying. Billroth II and Roux-en-Y reconstruction are superior to Billroth I and the use of a Braun enteroenterostomy in a classic Whipple has been shown to reduce delayed gastric emptying. Pancreaticojejunostomy and pancreaticogastrostomy are equivalent in their incidence of delayed gastric emptying and should be used according to a surgeon's preference.

Nutrition is important to improve a patient's outcome following surgery. If a patient has sarcopenia, then consideration should be made for a preoperative nutritional regime to improve their strength and reduce their risk of delayed gastric emptying. In the post-operative period, then the use of enteral or parenteral nutrition, together with metoclopramide and erythromycin has been shown to be beneficial.

Finally, patience from the surgeon is vital. Operative intervention is not indicated in the absence of any mechanical obstruction and can exacerbate the problem.

References

1. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg. 1988;207(1):39–47.
2. Miedema BW, Sarr MG, van Heerden JA, Nagorney DM, McIlrath DC, Ilstrup D. Complications following pancreaticoduodenectomy. Curr Manag Arch Surg. 1992;127(8):945–9; discussion 9–50.
3. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226(3):248–57; discussion 57–60.
4. Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. Dig Surg. 2001;18(6):453–7; discussion 8.
5. Gouma DJ, Nieveen van Dijkum EJ, Obertop H. The standard diagnostic work-up and surgical treatment of pancreatic head tumours. Eur J Surg Oncol. 1999;25(2):113–23.
6. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreatoduodenectomy. Is it an adequate cancer operation. Arch Surg. 1994;129(4):405–12.
7. Buchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. Br J Surg. 2000;87(7):883–9.
8. Tanaka M. Gastroparesis after a pylorus-preserving pancreatoduodenectomy. Surg Today. 2005;35(5):345–50.
9. Dong K, Yu XJ, Li B, Wen EG, Xiong W, Guan QL. Advances in mechanisms of postsurgical gastroparesis syndrome and its diagnosis and treatment. Chin J Dig Dis. 2006;7(2):76–82.
10. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761–8.
11. Malleo G, Crippa S, Butturini G, Salvia R, Partelli S, Rossini R, et al. Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: validation of international study Group of Pancreatic Surgery classification and analysis of risk factors. HPB (Oxford). 2010;12(9):610–8.
12. Welsch T, Borm M, Degrate L, Hinz U, Buchler MW, Wente MN. Evaluation of the international study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. Br J Surg. 2010;97(7):1043–50.
13. Tanaka M, Sarr MG. Role of the duodenum in the control of canine gastrointestinal motility. Gastroenterology. 1988;94(3):622–9.
14. Matsunaga H, Tanaka M, Naritomi G, Yokohata K, Yamaguchi K, Chijiwa K. Effect of leucine 13-motilin (KW5139) on early gastric stasis after pylorus-preserving pancreatoduodenectomy. Ann Surg. 1998;227(4):507–12.
15. Katagiri F, Itoh H, Takeyama M. Effects of erythromycin on plasma gastrin, somatostatin, and motilin levels in healthy volunteers and postoperative cancer patients. Biol Pharm Bull. 2005;28(7):1307–10.
16. Tanaka A, Ueno T, Oka M, Suzuki T. Effect of denervation of the pylorus and transection of the duodenum on acetaminophen absorption in rats; possible mechanism for early delayed gastric emptying after pylorus preserving pancreatoduodenectomy. Tohoku J Exp Med. 2000;192(4):239–47.
17. Gauvin JM, Sarmiento JM, Sarr MG. Pylorus-preserving pancreaticoduodenectomy with complete preservation of the pyloroduodenal blood supply and innervation. Arch Surg. 2003;138(11):1261–3.
18. Noorani A, Rangelova E, Del Chiaro M, Lundell LR, Ansorge C. Delayed gastric emptying after pancreatic surgery: analysis of factors determinant for the short-term outcome. Front Surg. 2016;3:25.
19. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing. 2010;39(4):412–23.

20. Joglekar S, Asghar A, Mott SL, Johnson BE, Button AM, Clark E, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol. 2015;111(6):771–5.
21. Tankel J, Dagan A, Vainberg E, Boaz E, Mogilevsky L, Hadas I, et al. Sarcopenia is associated with a greater incidence of delayed gastric emptying following pancreaticoduodenectomy. Clin Nutr ESPEN. 2018;27:105–9.
22. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet. 1978;146(6):959–62.
23. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy a follow-up evaluation. Ann Surg. 1980;192(3):306–10.
24. Kim DK, Hindenburg AA, Sharma SK, Suk CH, Gress FG, Staszewski H, et al. Is pylorospasm a cause of delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy? Ann Surg Oncol. 2005;12(3):222–7.
25. Fischer CP, Hong JC. Method of pyloric reconstruction and impact upon delayed gastric emptying and hospital stay after pylorus-preserving pancreaticoduodenectomy. J Gastrointest Surg. 2006;10(2):215–9.
26. Manes K, Lytras D, Avgerinos C, Delis S, Dervenis C. Antecolic gastrointestinal reconstruction with pylorus dilatation. Does it improve delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy? HPB (Oxford). 2008;10(6):472–6.
27. Uravic M, Zelic M, Petrosic N, Tokmadzic VS, Stimac D, Sustic A. Effect of pyloric dilatation on gastric emptying after pylorus-preserving pancreaticoduodenectomy. Hepatogastroenterology. 2011;58(112):2144–7.
28. Fujii T, Kanda M, Kodera Y, Nagai S, Sahin TT, Hayashi M, et al. Preservation of the pyloric ring has little value in surgery for pancreatic head cancer: a comparative study comparing three surgical procedures. Ann Surg Oncol. 2012;19(1):176–83.
29. Hackert T, Hinz U, Hartwig W, Strobel O, Fritz S, Schneider L, et al. Pylorus resection in partial pancreaticoduodenectomy: impact on delayed gastric emptying. Am J Surg. 2013;206(3):296–9.
30. Klaiber U, Probst P, Strobel O, Michalski CW, Dorr-Harim C, Diener MK, et al. Meta-analysis of delayed gastric emptying after pylorus-preserving versus pylorus-resecting pancreatoduodenectomy. Br J Surg. 2018;105(4):339–49.
31. Tran KT, Smeenk HG, van Eijck CH, Kazemier G, Hop WC, Greve JW, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg. 2004;240(5):738–45.
32. Goei TH, van Berge Henegouwen MI, Slooff MJ, van Gulik TM, Gouma DJ, Eddes EH. Pylorus-preserving pancreatoduodenectomy: influence of a Billroth I versus a Billroth II type of reconstruction on gastric emptying. Dig Surg. 2001;18(5):376–80.
33. Shimoda M, Kubota K, Katoh M, Kita J. Effect of billroth II or roux-en-Y reconstruction for the gastrojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled study. Ann Surg. 2013;257(5):938–42.
34. Busquets J, Martin S, Fabregat J, Secanella L, Pelaez N, Ramos E. Randomized trial of two types of gastrojejunostomy after pancreatoduodenectomy and risk of delayed gastric emptying (PAUDA trial). Br J Surg. 2019;106(1):46–54.
35. Hartel M, Wente MN, Hinz U, Kleeff J, Wagner M, Muller MW, et al. Effect of antecolic reconstruction on delayed gastric emptying after the pylorus-preserving Whipple procedure. Arch Surg. 2005;140(11):1094–9.
36. Nikfarjam M, Kimchi ET, Gusani NJ, Shah SM, Sehmbey M, Shereef S, et al. A reduction in delayed gastric emptying by classic pancreaticoduodenectomy with an antecolic gastrojejunal anastomosis and a retrogastric omental patch. J Gastrointest Surg. 2009;13(9):1674–82.
37. Oida T, Mimatsu K, Kano H, Kawasaki A, Fukino N, Kida K, et al. Antecolic and retrocolic route on delayed gastric emptying after MSSPPD. Hepatogastroenterology. 2012;59(116):1274–6.

38. Su AP, Cao SS, Zhang Y, Zhang ZD, Hu WM, Tian BL. Does antecolic reconstruction for duodenojejunostomy improve delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy? A systematic review and meta-analysis. World J Gastroenterol. 2012;18(43):6315–23.
39. Eshuis WJ, van Eijck CH, Gerhards MF, Coene PP, de Hingh IH, Karsten TM, et al. Antecolic versus retrocolic route of the gastroenteric anastomosis after pancreatoduodenectomy: a randomized controlled trial. Ann Surg. 2014;259(1):45–51.
40. Bell R, Pandanaboyana S, Shah N, Bartlett A, Windsor JA, Smith AM. Meta-analysis of antecolic versus retrocolic gastric reconstruction after a pylorus-preserving pancreatoduodenectomy. HPB (Oxford). 2015;17(3):202–8.
41. Qiu J, Li M, Du C. Antecolic reconstruction is associated with a lower incidence of delayed gastric emptying compared to retrocolic technique after Whipple or pylorus-preserving pancreaticoduodenectomy. Medicine (Baltimore). 2019;98(34):e16663.
42. Hochwald SN, Grobmyer SR, Hemming AW, Curran E, Bloom DA, Delano M, et al. Braun enteroenterostomy is associated with reduced delayed gastric emptying and early resumption of oral feeding following pancreaticoduodenectomy. J Surg Oncol. 2010;101(5):351–5.
43. Mehrdad Nikfarjam NH, Tufail F, Weinberg L, Muralidharan V, Christophi C. Reduction in delayed gastric emptying following non-pylorus preserving pancreaticoduodenectomy by addition of a Braun enteroenterostomy. J Pancreas. 2012;13(5):488–96.
44. Watanabe Y, Ohtsuka T, Kimura H, Matsunaga T, Tamura K, Ideno N, et al. Braun enteroenterostomy reduces delayed gastric emptying after pylorus-preserving pancreatoduodenectomy: a retrospective review. Am J Surg. 2015;209(2):369–77.
45. Fujieda H, Yokoyama Y, Hirata A, Usui H, Sakatoku Y, Fukaya M, et al. Does Braun anastomosis have an impact on the incidence of delayed gastric emptying and the extent of intragastric bile reflux following pancreatoduodenectomy?—a randomized controlled study. Dig Surg. 2017;34(6):462–8.
46. Zhou Y, Hu B, Wei K, Si X. Braun anastomosis lowers the incidence of delayed gastric emptying following pancreaticoduodenectomy: a meta-analysis. BMC Gastroenterol. 2018;18(1):176.
47. Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg. 2005;242(6):767–71; discussion 71–3.
48. Lyu Y, Li T, Cheng Y, Wang B, Chen L, Zhao S. Pancreaticojejunostomy versus Pancreaticogastrostomy after Pancreaticoduodenectomy: an up-to-date meta-analysis of RCTs applying the ISGPS (2016) criteria. Surg Laparosc Endosc Percutan Tech. 2018;28(3):139–46.
49. Parmar AD, Sheffield KM, Vargas GM, Pitt HA, Kilbane EM, Hall BL, et al. Factors associated with delayed gastric emptying after pancreaticoduodenectomy. HPB (Oxford). 2013;15(10):763–72.
50. Beane JD, House MG, Miller A, Nakeeb A, Schmidt CM, Zyromski NJ, et al. Optimal management of delayed gastric emptying after pancreatectomy: an analysis of 1,089 patients. Surgery. 2014;156(4):939–46.
51. Hu HL, Zhou XD, Zhang Q, Shi X. Factors influencing delayed gastric emptying after pancreaticoduodenectomy—a meta-analysis. Hepatogastroenterology. 2014;61(134):1539–45.
52. Liu QY, Li L, Xia HT, Zhang WZ, Cai SW, Lu SC. Risk factors of delayed gastric emptying following pancreaticoduodenectomy. ANZ J Surg. 2016;86(1–2):69–73.
53. Perkel MS, Moore C, Hersh T, Davidson ED. Metoclopramide therapy in patients with delayed gastric emptying: a randomized, double-blind study. Dig Dis Sci. 1979;24(9):662–6.
54. Yeo CJ, Barry MK, Sauter PK, Sostre S, Lillemoe KD, Pitt HA, et al. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. Ann Surg. 1993;218(3):229–37; discussion 37–8.
55. Kollmar O, Moussavian MR, Richter S, de Roi P, Maurer CA, Schilling MK. Prophylactic octreotide and delayed gastric emptying after pancreaticoduodenectomy: results of a prospective randomized double-blinded placebo-controlled trial. Eur J Surg Oncol. 2008;34(8):868–75.

56. Braga M, Pecorelli N, Ariotti R, Capretti G, Greco M, Balzano G, et al. Enhanced recovery after surgery pathway in patients undergoing pancreaticoduodenectomy. World J Surg. 2014;38(11):2960–6.
57. Sutcliffe RP, Hamoui M, Isaac J, Marudanayagam R, Mirza DF, Muiesan P, et al. Implementation of an enhanced recovery pathway after pancreaticoduodenectomy in patients with low drain fluid amylase. World J Surg. 2015;39(8):2023–30.
58. Dai J, Jiang Y, Fu D. Reducing postoperative complications and improving clinical outcome: enhanced recovery after surgery in pancreaticoduodenectomy—a retrospective cohort study. Int J Surg. 2017;39:176–81.

Chapter 70
Uncommon and Rare Complications After Pancreatic Surgery

Alex Nicolas Gordon-Weeks, Daniel Llwyd Hughes, and Michael A. Silva

Take Home Messages

- Always maintain high index of suspicion for complications after pancreatic surgery and early rescue is mandatory to ensure good outcomes
- Early complications include bleeding, fistula, and thrombosis
- Arterial injuries are rare but may have grave consequences
- Rare complications can co-exist alongside more common complications and their presence can therefore be overlooked.
- A herald gastrointestinal bleed after pancreatoduodenectomy is due to a GDA stump blow-out until proven otherwise
- Long-term complications include risk of diabetes and anastomotic strictures

Pearls and Pitfalls

- Beware of possible arterial anatomy variations; study good quality arterial phase CT in pre-operation staging
- In patients with no pre-operative biliary stent and with a normal pancreatic duct, the gland is likely to be soft and at higher risk of anastomotic failure
- It is possible to sacrifice an aberrant right hepatic artery that arises from the SMA which is involved by tumour, by embolising it prior to surgery to establish collateral supply to right liver from the left hepatic artery
- An omental wrap of the pancreatic anastomosis may not reduce the incidence of leaks but may protect the GDA stump and prevent false aneurysms and post operative bleeding

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70.1 Introduction

Pancreatic surgery is associated with significant morbidity of 30–40% [1]. Although 30-day mortality has declined over the last 2 decades to 2–5%, operative technique and perioperative care [2], morbidity remains a major challenge.

Complications following pancreatic surgery primarily relates to pancreatic fistula [2]. Additionally, a range of less-common complications do occur (Table 70.1). These complications are wide ranging because of the organ's structural biology, its close proximity to major blood vessels and associated viscera, variations in hepatobiliary anatomy between patients and the high degree of technical fidelity required to perform pancreatic resections.

This chapter attempts to cover less frequently encountered complications of pancreatic surgery based on the available literature and the authors personal experiences. Most of these are life-threatening, significantly prolong hospital stay, frequently with intensive care input and are an economic burden to the healthcare system [3]. In general, they can co-exist alongside more common complications and their presence can therefore be overlooked. Their management typically requires a multi-disciplinary approach with early identification and rapid rescue that can improve outcome. An understanding of the ways in which they may present and the principles of their management is therefore paramount.

70.2 Vascular Complications

Vascular complications such as major secondary post-operative haemorrhage typically occur on the background of pancreatic anastomotic leak (discussed elsewhere in this book).

Table 70.1 Case reports of pancreatic surgery complications

Complication	Operation	Presentation	Management
Septic arthritis [64]	Distal pancreatectomy	Sepsis	Irrigation, antibiotics
Bronchopulmonary fistula [65]	Pancreatoduodenectomy	Bilioptysis 10-years post-op	IR-guided therapy
Portal vein pseudoaneurysm [66]	Pancreatoduodenectomy	Upper GI bleed	IR-guided therapy
Portoenteric fistula [66]	Pancreatoduodenectomy	Upper GI bleed	Operative intervention
Diaphragmatic hernia [67]	Distal pancreatectomy and splenectomy	Abdominal pain	Operative intervention
Hepatic lymphorrhea [68]	Total pancreatectomy	Massive ascites	Open drainage
Dorsal pancreatic arcade haemorrhage [69]	Pancreatoduodenectomy	Sentinel bleed	IR-guided therapy
Arteriobiliary fistula [70]	Pancreatoduodenectomy	Shock, haemobilia	IR-guided therapy

70.3 Arterial Injuries

Injury to specific vessels are rare (<0.9% in one series) [4], but can occasionally present as an isolated problem. Pre-operative arterial, venous and portal phase imaging is crucial for identifying variants in vascular anatomy and tumour involvement. Understanding these factors and using this knowhow to plan the operative approach is most likely to identify patients at risk of and ultimately prevent vascular injury. Notably, arterial injuries in particular are invariably associated with adverse outcome, prolonged intensive care stay and reduced survival [5].

70.3.1 Superior Mesenteric Artery (SMA) Injury

This potentially devastating complication is thankfully rare and is typically encountered during surgery for pancreatic head malignancy. Injury may involve complete arterial transection, serosal injury or intimal injury that can occur following operative manipulation and close dissection. Transection injuries are usually identified and repaired at the time of surgery. Serosal or intimal injuries have potential to result in false aneurysms and can present in the post-operative period with major haemorrhage due to rupture, especially when associated with a pancreatic fistula. An alternative presentation is with mid-gut ischaemia secondary to thrombosis.

Symptoms resulting from complication of intimal injuries may mimic standard post-operative discomfort and the clinician will require a high index of suspicion. Patients with severe pain out of proportion to the physical examination and a rising lactate despite adequate fluid resuscitation should be reviewed early and usually will require urgent CT angiography. Delays in identification of this complication risks complete loss of the midgut territory bowel due to ischaemia with the need for life-long peripheral nutrition and/or in a small proportion of patients who may be eligible, small intestinal transplantation.

Definitions of pancreatic cancer operability may have helped to reduce the incidence of SMA injuries by identifying those patients with arterial involvement prior to surgery [6]. Borderline resectable tumours with SMA involvement may have a higher risk of SMA injury and use of an arterial-first approach in these cases enables an early appreciation of the risk of SMA injury if resection is to be attempted [7]. In any patient deemed at risk based on pre-operative imaging or artery-first dissection, proximal control of the SMA prior to dissection of the pancreas is beneficial to control torrential haemorrhage should injury occur [8].

Complete transection injuries are treated with end-to-end anastomosis or with use of an intervening autologous vein or synthetic graft if anastomotic tension is an issue [7]. An alternative approach is re-implantation of the distal SMA to the infrarenal aorta and this may help reduce post-anastomotic stricture development, which is frequently seen following end-to-end SMA repair (Fig. 70.1) [8, 9]. Literature from patients undergoing planned SMA reconstruction in the setting of advanced pancreatic malignancy indicates an association with significant intra-operative

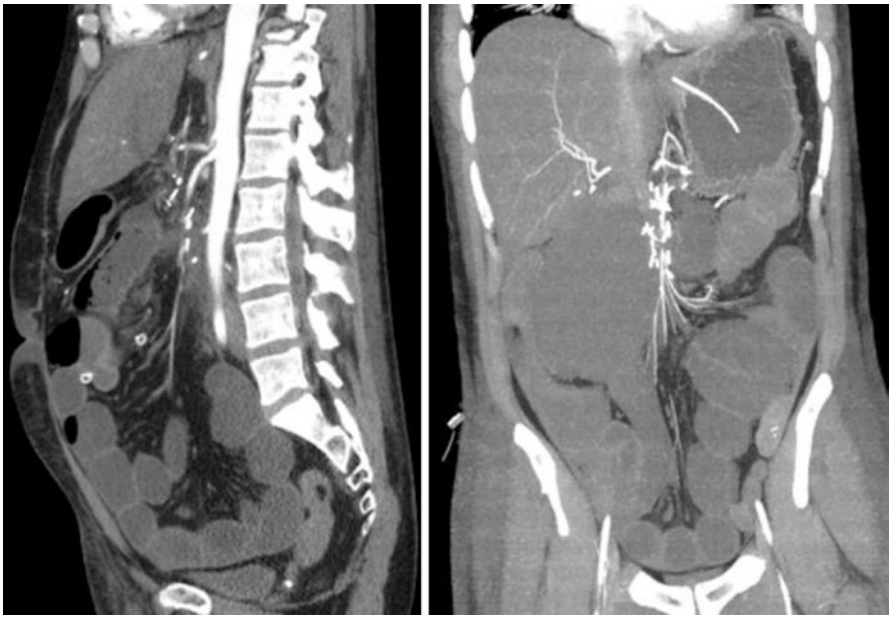

Fig. 70.1 Transection injury of SMA at total pancreatectomy repaired with end-to-end anastomosis. Arterial-phase CT demonstrating post-operative thrombosis of the repair end-to-end SMA anastomosis with bowel ischaemia resulting from evident but insufficient arterial backfilling from the IMA. The patient ultimately required enterectomy to the distal transverse colon. The bile duct was anastomosed to the pylorus of the stomach and a venting gastrostomy placed. The patient is currently on the bowel transplant waiting list as his pancreas histology was benign

blood loss and poor post-operative outcome, with twice the expected 30-day mortality compared with standard pancreatic resections [8–10]. This should be borne in mind in patients who undergo repair of SMA injury who will require close monitoring and assessment of coagulation status using thromboelastography to guide the judicious use of anticoagulant agents in the post-operative period. Typically, these patients will be managed in an intensive care setting.

70.3.2 Hepatic Artery and Coeliac Trunk Injuries

The strongest predictor of hepatic arterial injury is aberrant arterial anatomy. The hepatic artery (HA) in particular demonstrates significant patient-to-patient variation. The presence of a replaced or accessory right HA (RHA) arising from the SMA is the most common variant [11, 12] with other variants including replaced or accessory left hepatic arteries particularly from the left gastric is also recognised [13]. The replaced RHA usually travels posterior to the portal vein from the SMA and this must be safeguarded to prevent injury during division of retro-portal tissue during pancreatic head resection [7].

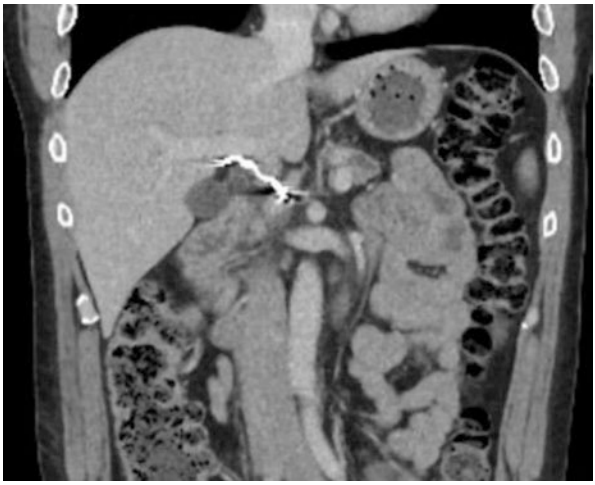

Fig. 70.2 Selective pre-operation embolisation of fully replaced right hepatic artery. This was required prior to Whipples procedure for pancreatic head malignancy. The patient experienced successful collateralisation and underwent an uncomplicated pancreatectomy

In some cases, either due to local invasion, or because the replaced RHA arises from an intra-pancreatic portion of the SMA, the artery may need to be sacrificed to achieve satisfactory disease clearance. Performing an artery-first approach is useful for identification of such cases. Reconstruction of the injured RHA may be attempted through use of saphenous vein or artificial interposition grafts, although the diameter of the vessel usually does not make such repair suitable and post repair thrombosis is common. An alternative approach is to sacrifice the RHA [14]. Indeed, this approach has potential advantages over attempted reconstruction including less blood loss and lack of post-operative anastomotic complications. Our practice is to selectively embolise a replaced RHA arising from the SMA if it requires sacrifice due to tumour involvement, 2 weeks prior to surgery. This enables establishment of collateralisation of the right lobe via the left hepatic artery. Prior to embolisation, the presence of right-left communication is established by formal selective angiography (Fig. 70.2).

Although in cases of intra-operative RHA injury, the liver can survive through portal oxygenation and significant collateral supply from other sources [14], these patients typically develop ischaemic hepatitis following loss of arterial supply [15, 16]. The typical presentation is with right upper quadrant pain and deranged liver function tests, notably with raised transaminase enzymes. Evidence of hepatic ischaemia should be recorded using arterial-phase cross-sectional imaging and serial imaging may be required to monitor progression of the ischaemic insult. Although in the majority of patients this is self-resolving (Fig. 70.3) [14], the presence of septic features could indicate the development of hepatic abscess which may require percutaneous drainage. Rarely, partial hepatectomy may be required in these cases.

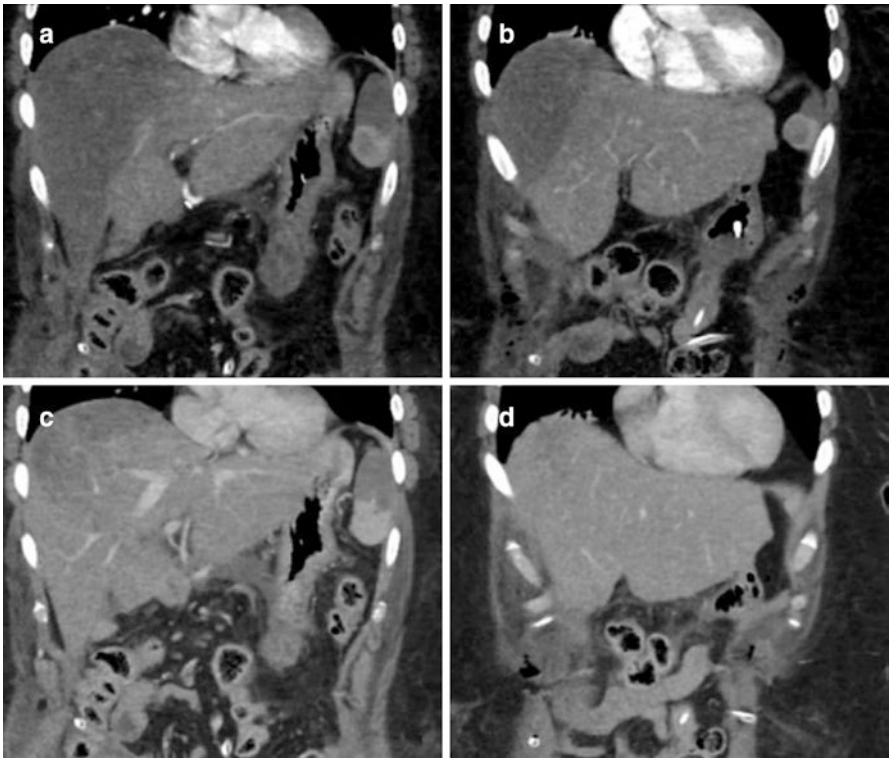

Fig. 70.3 Inadvertent right hepatic artery transection causing right hepatic ischaemia. (**a**, **b**) Day 1 post-op arterial phase CT abdomen demonstrating reduced perfusion to the right hemi-liver. (**c**, **d**) Day 10 post-op showing improved arterial enhancement in the right hemi-liver with development of collaterals

70.3.3 Post-Operative Pancreatic Haemorrhage

Post-operative pancreatic haemorrhage (PPH) occurs in 3–5% of patients following pancreatic resection [17–20]. Bleeding is often associated with major (grade C) pancreatic fistula. PPH is associated with a mortality of up to 20% [21]. Various attempts to classify PPH including division into intra- vs extra-luminal haemorrhage [17] or presentation <24 h vs >24 h post-surgery [19] have been utilised to identify likely aetiology and guide management.

70.3.4 Clinical Presentation of Bleeding

The typical presentation is with sudden haemodynamic compromise and associated signs of a GI bleed or blood in peritoneal drains. An early brisk bleed that spontaneously stops prior to becoming a large haemorrhage occurs in up to 70% of patients

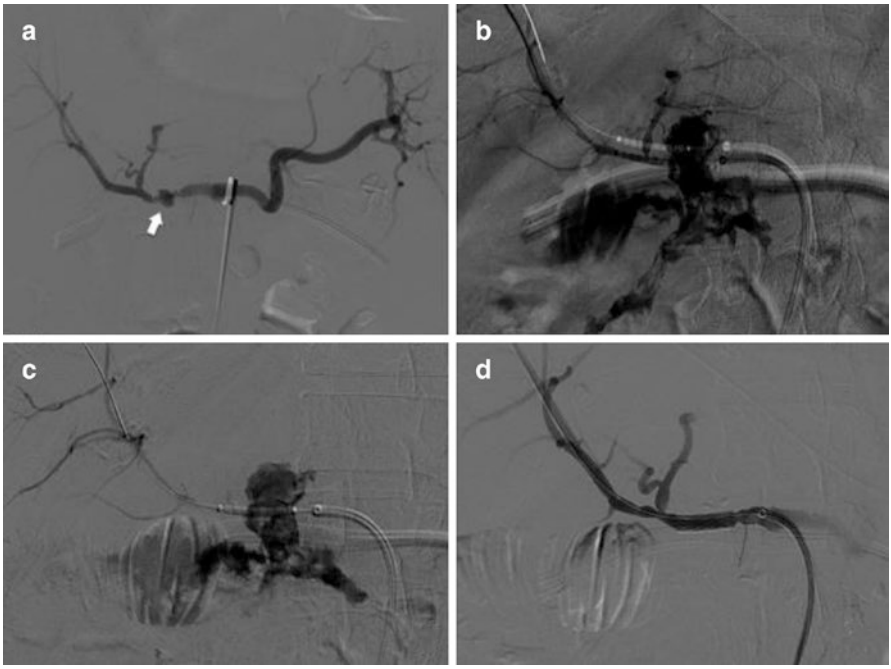

Fig. 70.4 Imaging findings in patient with Herald bleed following pancreatectomy. (**a**) Selective coeliac artery angiography showing GDA stump false aneurysm. (**b**, **c**) Placement of stent within common hepatic artery aneurysm with extravasating contrast demonstrating how blood from GDA reached jejunum. (**d**) Control of bleed following satisfactory stent placement in common hepatic artery

with PPH [20, 22] and more common in late bleeds. A herald bleed, when it occurs, presents as an enteral bleed (haematemesis or coffee ground vomitus or melena). Here the bleed is initially intra-abdominal from a false aneurysm originating from the gastroduodenal artery stump which makes its way through the defect in the pancreatico- enteral anastomosis to reach the GI tract as a herald bleed (Fig. 70.4).

Early PPH is more likely to be cause by bleeding from the SMA in patients who have undergone pancreatic head resection, or the splenic artery in the case of distal pancreatic resections. Conversely, late PPH is primarily caused by hepatic territory or gastroduodenal artery (GDA) stump 'blow outs' [19, 20].

Because of the association between major pancreatic fistula and late haemorrhage, the authors preference is to fashion an omental wrap around the pancreaticojejunal anastomosis following pancreatic head resection as a means of safeguarding the divided remnant GDA and right gastric artery stump should an anastomotic leak develop. Careful GDA transfixion with a non-absorbable suture and the application of multiple clips or ties to the GDA stump are other methods that the authors routinely employ to reduce PPH. At surgery, it is also our practice to leave a relatively long GDA stump in place to facilitate post-operative embolisation should haemorrhage occur.

If the GDA stump is short the management of a GDA blow out and false aneurysm is through interventional radiological stent placement in the common hepatic

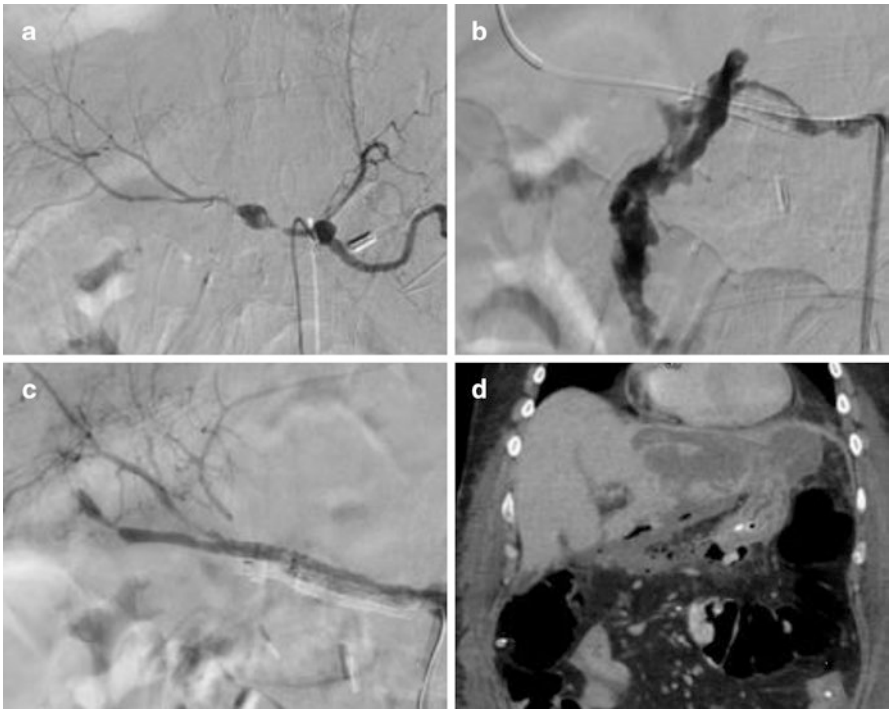

Fig. 70.5 Pitfalls in the management of GDA false aneurysm. This patient developed a GDA false aneurysm secondary to a pancreatic anastomotic leak post Whipples procedure. (**a**). On deployment of the stent in the common hepatic artery at the level of the GDA origin, there was immediate massive extravasation of blood due to rupture of the vessel (**b**). The interventional radiologist immediately deployed another stent beyond the level of the rupture and controlled the bleeding, securing the GDA false aneurysm (**c**). However, this second stent also occluded the left hepatic artery origin. The patient developed segment II/III ischaemia and later a liver abscess which was managed with a radiological drain (**d**). This patient remains well 4 years post-surgery

artery occluding the GDA origin. Placement of common hepatic artery stents are not always straightforward due to natural kinks in the artery and availability of suitably size matched stents. In the setting of a pancreatic leak and local sepsis, the common hepatic artery is also friable at the level of the GDA origin and minor diameter size match discrepancies can result in common hepatic artery rupture at stent deployment (Fig. 70.5). Patients with PPH require the co-ordinate management of HPB surgeons, radiologists, intensive care physicians and haematologists.

70.3.5 Portal Vein Thrombosis

Portal vein thrombosis (PVT) occurs in approximately 5% of patients undergoing portal vein reconstruction [23, 24]. The presentations of this rare complication include non-specific abdominal pain, nausea and fevers as well as haemodynamic collapse

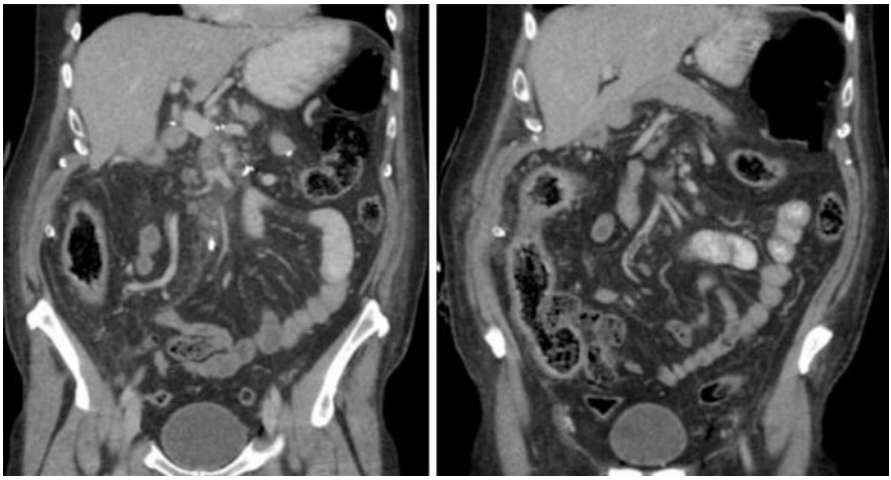

Fig. 70.6 Complicated portal vein thrombus. Portal venous-phase CT abdomen demonstrating portal vein thrombus (left) with resultant thickening and paracolic fat stranding of the ascending colon indicating ischaemia (right) in a patient 8-days following Whipples procedure with portal vein lateral venorrhaphy. This presented 8-days following surgery and was associated with theombocytopenia. A diagnosis of heparin-induced thrombocytopenia was diagnosed. The patient was anticoagulated with fondaparinux and his condition improved without further intervention

and bloody diarrhoea secondary to intestinal ischaemia. Later presentations include ascites, splenomegaly and upper gastrointestinal bleeding from varices. Early cross-sectional imaging with multi-phase CT is important for delineating the degree of venous occlusion and to look for evidence of bowel ischaemia. Although Doppler ultrasound has a reported sensitivity and specificity of 93% and 99% respectively compared to 90% and 99% for contrast computer tomography in the diagnosis of PVT [25, 26], CT has the benefit of being able to detect the presence of co-existent complications. The predominant risk factor for PVT is portal vein reconstruction (Fig. 70.6). Patients who undergo PTFE re-construction as opposed to renal vein interposition graft or lateral venorrhaphy alone are at the greatest risk of thrombosis [24].

70.3.6 Management of Portal Venous Thrombosis

Management is dependent upon the severity of thrombotic complications and the duration of symptoms, with early thrombus being most amenable to anticoagulation or thrombolytic therapies. Published evidence to guide management is particularly weak and based primarily on patients treated for spontaneous PVT not related to surgery. Here, early administration of systemic heparin enables re-canalisation in up to 50% of patients and lowers the subsequent incidence of PVT complications including portal hypertension, splenomegaly and collateral formation [27]. The benefit of systemic heparin is supported by small series of patients who develop PVT following pancreatectomy [28].

For patients in whom re-canalisation is not achieved through systemic anticoagulation or for patients with acute venous ischaemia, the next option is catheter directed thrombolytic therapy delivered via the portal vein or SMV. In the setting of anastomotic stricture, radiological stent placement has been successful in preventing recurrent thrombosis on rare occasions following catheter directed thrombolytic therapy. Although this technique has a greater re-canalisation rate than systemic heparin this is only the case if it is used within the first 2 weeks of PVT formation [29], significantly limiting its utilisation in the post-operative period.

An alternative approach in patients with acute intestinal ischaemia secondary to PVT is to perform operative thrombectomy. This approach has been reported in patients with bowel ischaemia following pancreatic surgery with successful removal of PVT clot and preservation of the intestine [30].

70.4 Non-vascular Complications

70.4.1 Stent-Related Complications of the Pancreatico-Jejunal Anastomosis

Plastic stents are frequently used in the pancreatico-jejunal anastomosis with the intention being to aid pancreatic drainage, promote anastomotic healing and ultimately reduce the incidence of clinically relevant post-operative pancreatic fistula (POPF).

Pancreatic stent placement has also been attributed to post-operative complication. Potential problems include stent retention and migration although it is not possible to determine the incidence of these complications from the published literature due to the possibility of under-reporting. Stent retention presents with steatorrhoea and/or recurrent post-operative pancreatitis [31, 32]. Endoscopic removal of the stent is indicated if it is found to be retained at 6-months post-surgery [33], or sooner if resulting in complication. Interestingly, in those cases reporting stent retention, the plastic stent was not identified on cross-sectional imaging (CT or MRI) [32] indicating need for clear documentation of stent use at the time of surgery. Pancreatic stent migration was the underlying aetiological factor in patients presenting with intestinal bezoar obstruction [34, 35] perforation requiring bowel resection [36] and hepatic abscess [37].

70.4.2 Post-Pancreatectomy Pancreatitis

Diagnosis of post-pancreatectomy pancreatitis (PPP) is complicated by the significant overlap in presentation with POPF. Under certain circumstances POPF may be the direct result of PPP as indicated by studies demonstrating that post-operative

pancreatic inflammation pre-dates POPF [38, 39]. This is further supported by histological evidence of pancreatitis and pancreatic necrosis in pancreatic remnant explants from patients with grade C POPF [40]. However, documentary evidence of serum lipase and amylase rises in the absence of subsequent POPF [41, 42] indicate that PPP may also exist as a clinical entity separate to POPF [43]. The aetiology of PPP includes ischaemia, perfusion abnormality, gland texture and intra-operative trauma [43].

70.4.3 Bilioenteric Anastomotic Complications

The bilioenteric anastomosis can be complicated by either leak (early) or stricture (late). Both complications are relatively rare.

70.4.4 Bile Leaks

Clinically relevant bile leak occurs in <1% of patients. It usually presents within the first week of surgery with an elevated drain bilirubin alone or with ensuing biliary peritonitis, sepsis and multi-organ failure [44, 45]. Small biliary duct diameter [46, 47] and coeliac axis atherosclerosis [47] are the primary risk factors and most biliary leaks occur with concomitant POPF. Intra-abdominal haemorrhage is also frequently seen in patients with anastomotic leak indicating the importance of concurrent arterial-phase imaging in the work-up of these patients [46].

At least 50% of patients with biliary anastomotic leak will settle spontaneously with conservative management consisting of prolonged drainage and antibiotics [44, 45]. Patients with evidence of peritonitis, a large volume of free intra-peritoneal fluid or rising inflammatory markers are better served with early laparotomy, copious washout and re-fashioning of the anastomosis around a T-tube.

Complete disruption of the bilioenteric anastomosis is rare and can be associated with re-laparotomy for POPF. This usually requires re-fashioning of the anastomosis over a T-tube. At re-do anastomosis, the cut surface of the bile duct is usually inflamed and fragile and this may require further excision to the level of healthy duct. This may go beyond the bile duct confluence and result in two ducts to anastomose, increasing the complexity. Another option in this situation is to place the limbs of a T-tube in the right and left ducts with the tube itself crossing the anastomosis to be externalised through the jejunal wall further downstream (Fig. 70.7). The anastomosis is then secured with interrupted absorbable sutures that also include the hilar plate along with the bile duct wall thus preventing the sutures ‘cheese wiring’ through the friable tissue. A wide bore drain is also left in the subhepatic space to cover the inevitable bile leak.

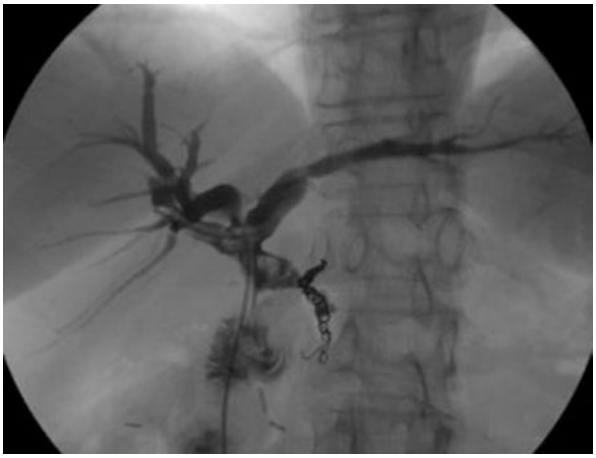

Fig. 70.7 Bilioenteric disruption. Cholangiogram demonstrating complete breakdown of bilioenteric anastomosis. This was managed with re-laparotomy trimming back of bile duct to the hilar plate and placement of the limbs of a T-tube in the right and left ducts with the tube itself crossing the anastomosis to be externalised through the jejunal wall further downstream and then exteriorised via the anterior abdominal wall

70.4.5 Bile Duct Stricture

The incidence of biliary anastomotic stricture following pancreatoduodenectomy is reported at approximately 3% [22, 44, 48, 49]. Early and late subtypes are identified. *Early strictures* present within the first weeks of surgery, whilst the average time to presentation of *late strictures* is 12 months. Bile duct diameter ≤5 mm is an independent predictor for early stricture development [44]. Conversely, aetiological factors in late strictures include the use of pre-operative biliary drainage and age <60 years [22, 48]. The primary pathology (benign vs malignant disease) does not affect the incidence of biliary anastomotic stricture and although adjuvant chemotherapy is also not a risk factor, the use of adjuvant radiotherapy is strongly associated with stricture formation [49].

Patients with rising bilirubin, recurrent cholangitis or choledocholithiasis following pancreatic surgery should initially undergo ultrasonographic examination. Biliary dilatation in a jaundiced patient is an indication for further imaging. Magnetic resonance cholangiopancreatography is the modality of choice, as it provides an unparalleled level of ductal anatomical detail and detection of concurrent biliary leaks [50].

For late strictures in patients who have undergone pancreatic cancer surgery, positron-emission CT (PET) scan is useful to exclude malignant recurrence at the anastomotic site, although in the setting of cholangitis PET will have a high false-positive rate and should be delayed until any sepsis has resolved. Biliary scintography, although useful in the evaluation of leak, is not sensitive or specific for the detection of anastomotic stricture and does not delineate biliary tree anatomy sufficiently to plan management [51].

70.4.6 Management

For early strictures, surgery and re-fashioning of the anastomosis, preferably around a T-tube should be considered shortly after a stricture is detected. This management strategy is optimal, as early stricture typically involves technical failure which is best addressed operatively [44]. Patients with cholangitis will require urgent biliary de-compression pre-operatively and this is best performed through placement of a percutaneous transhepatic drainage tube as endoscopic approaches are unlikely to access the biliary anastomosis in patients who have undergone pancreatic surgery.

Interventional radiology is the primary therapeutic modality for patients with late-presenting anastomotic biliary stricture. Balloon dilatation and stent placement is performed via the percutaneous transhepatic route. Multiple interventions are usually required over a prolonged time period and therapeutic failure without evidence of recurrent malignancy will necessitate operative anastomotic revision. Prior to embarking on re-exploration for re-do biliary reconstruction, it is always helpful to carry out a CT angiogram to ascertain the anatomical location of the hepatic arteries in relation to the bile duct and anastomosis in order to avoid iatrogenic injury. Additionally, the presence of a PTC drain or stent is helpful in locating to bile duct at the hilum by palpation, especially if there is increased postoperative fibrosis.

70.4.7 Abdominal Wall Failure in the Setting of High Enteric Fistulae

Abdominal wall failure in the setting of pancreatectomy typically arises following damage control surgery for complex pancreatic or biliary fistulae. Re-look laparotomy in these patients leaves an abdomen that is difficult to close without undue tension due to intestinal distension, gut wall oedema, gross contamination and ascites. The primary aim is to close the fascial defect as quickly as possible. This task can be complicated by the presence of high-output enteric fistulae.

Negative pressure dressings (VAC dressings) to manage an open abdomen in this setting has proved invaluable. Commercially available negative pressure dressing systems like Abthera™ can be utilised with low settings to help reduce the incidence of suction related bowel fistulae. This strategy however is not feasible in the setting of an ongoing fistula especially if it is of high output. To overcome this it is usually possible to place large bore T-Tubes or Foley catheters (Fig. 70.8) in to the fistulating viscus and where possible exteriorising these tubes through the abdominal wall to divert flow of the fistula from the open abdomen, facilitates use of such dressing. In order to reduce loss of negative pressure around the exit sites of such drains, placement beyond the dressings or fashioning ‘chimney barriers’ around the Foley catheter or T-tube are measures commonly used (Fig. 70.8).

In some circumstances, diversion of the high output fistulae is not possible. In such situations the use of VAC dressing is not an option. These patients are managed

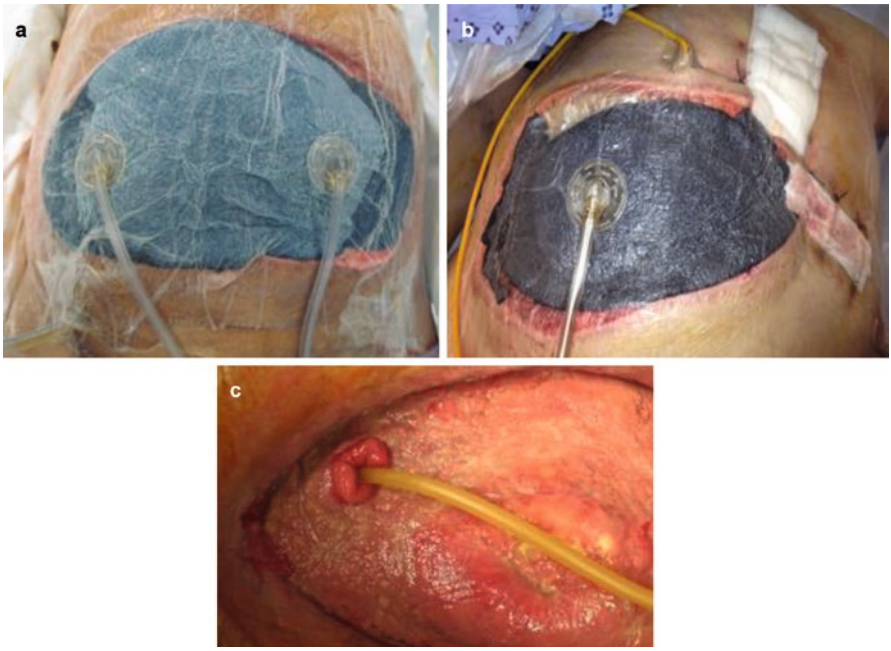

Fig. 70.8 Management of abdominal wall failure following pancreatectomy. (**a**) Negative pressure dressing for an open abdomen placed at re-laparotomy for sepsis post pancreatectomy. (**b**) T-tube placement (yellow) in a anastomotic leak with a 'chimney barrier' to facilitate use of a negative pressure dressing system. (**c**) Foley catheter under gentle traction to occlude enterotomies following anastomotic breakdown to divert high output fistulae and facilitate placement of negative pressure dressings to the healing abdominal wound. The goal is to eventually achieve skin cover and optimise patient sufficiently to subsequently re-explore and close fistulae

with large wound manager dressings with emphasis on sepsis control, overcoming organ dysfunction and planned re-exploration.

70.5 Long-Term Complications After Pancreatic Resection

Whilst most complications following pancreatic surgery occur within the immediate post-operative setting, a small proportion of which may have a delayed presentation and present several years post operatively.

70.5.1 Post-Pancreatectomy Diabetes

Endocrine failure in the remnant pancreas with subsequent development of pancreatogenic diabetes mellitus is an acknowledged late complication [52]. The incidence rates of new onset diabetes following pancreatic resection vary across the literature,

ranging from 0–50% [53–56]. A published case series of 1717 patients who underwent pancreatic surgery, noted a new onset diabetes rate of 30% following distal pancreatectomy, and a lower rate of 17%, following pancreaticoduodenectomy [56]. Predominance of islet cells within the pancreatic tail which may explained the observed higher rates of new onset diabetes following distal pancreatectomy [57].

70.5.2 Anastomotic Strictures

All gastro-intestinal anastomoses are vulnerable to the development of an anastomotic stricture over time. In the context of pancreatic surgery, pancreaticojejunal anastomotic stricture has been described as a late complication [58, 59]. There is a scarcity of literature on this topic. This is likely due to the fact that the vast majority of patients undergoing a pancreaticoduodenectomy is on the basis of a confirmed or suspected malignancy, these patients will succumb to their disease prior to developing a symptomatic pancreaticojejunal stricture. As there is now greater numbers of patients with benign disease undergoing pancreaticoduodenectomy, long-term follow up of this cohort has provided further insight into the symptomatic presentation of pancreaticojejunal stricture and potential treatment strategies [60]. The presentation often includes vague symptoms such as epigastric pain, nausea and weight-loss [61]. A published case series on 7 patients with symptomatic pancreaticojejunal stricture, noted that 71% of the cohort presented with recurrent pancreatitis [61].

Stone formation within the stricture may also contribute to the symptoms [62] (Fig. 70.9). If a pancreaticojejunal stricture is suspected, cross-sectional imaging should be organised to assess for stone impaction, stricture formation and subsequent upstream dilatation of the pancreatic duct. If the index pancreatic resection was for malignancy, excluding a localised recurrence should be considered. A PET

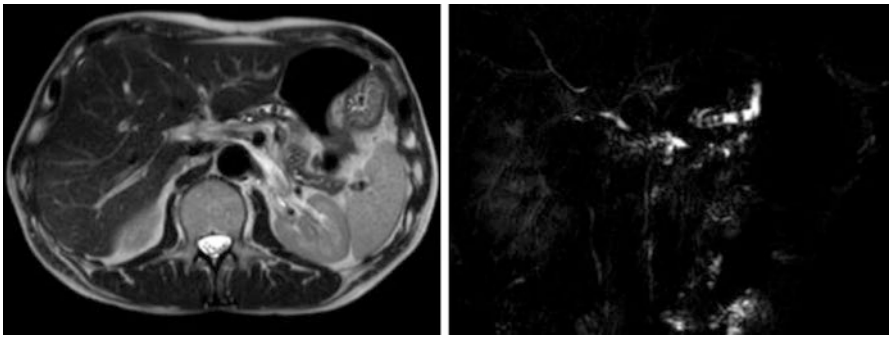

Fig. 70.9 Pancreaticojejunal stricture. MRI scan showing dilated pancreatic duct which contains multiple calculi with a stricture at pancreatojejunal anastomosis (right). MRCP of same patient demonstrating dilated duct and stones (left). This patient had a Whipples procedure for focal pancreatitis in the head of pancreas and developed this complication 4 years later. He also is having recurrent pancreatitis in his pancreatic remnant and is currently being assessed for potential completion pancreatectomy and islet auto transplantation

scan may be of benefit within this context. Management strategies for pancreaticojejunal strictures range from an endoscopic approach to surgical revision of the anastomosis [63].

70.6 Conclusion

Some of the less common complications following pancreatic surgery are presented here. These complications present acutely and are often associated with significant morbidity and mortality. The evidence base for the optimal management strategies for these complications is limited and is often based on individual case reports and single surgeon's experience. A low threshold for investigation is required in this unique patient cohort. Failure to identify such a complication and a delayed intervention is detrimental. Despite these complications being uncommon, they should not be managed in isolation by one team. Rather a true multi-disciplinary approach spanning several different specialities is required in order to improve individual patient outcomes.

References

1. Gouillat C, Gigot JF. Pancreatic surgical complications—the case for prophylaxis. Gut. 2001;49(Suppl 4):iv32–9.
2. Ho C-K, Kleeff J, Friess H, Büchler MW. Complications of pancreatic surgery. HPB (Oxford). 2005;7:99–108.
3. Kagedan DJ, Devitt KS, Tremblay St-Germain A, Ramjaun A, Cleary SP, Wei AC. The economics of recovery after pancreatic surgery: detailed cost minimization analysis of an enhanced recovery program. HPB (Oxford). 2017;19:1026–33.
4. Kleive D, Sahakyan MA, Khan A, Fosby B, Line P-D, Labori KJ. Incidence and management of arterial injuries during pancreatectomy. Langenbecks Arch Surg. 2018;403:341–8.
5. Kim AW, McCarthy WJ, Maxhimer JB, Quiros RM, Hollinger EF, Doolas A, Millikan KW, Deziel DJ, Godellas CV, Prinz RA. Vascular complications associated with pancreaticoduodenectomy adversely affect clinical outcome. Surgery. 2002;132:738–44; discussion 744–7.
6. Padilla Valverde D, Villarejo Campos P, Villanueva Liñán J, Menéndez Sánchez P, Cubo Cintas T, Martín Fernández J. Radiological-surgical methods to identify celiac-mesenteric anomalies of the hepatic artery before duodenopancreatectomy. Cir Esp. 2013;91:103–10.
7. Pallisera A, Morales R, Ramia JM. Tricks and tips in pancreatoduodenectomy. World J Gastrointest Oncol. 2014;6:344–50.
8. Amano H, Miura F, Toyota N, et al. Is pancreatectomy with arterial reconstruction a safe and useful procedure for locally advanced pancreatic cancer? J Hepatobiliary Pancreat Surg. 2009;16:850–7.
9. Jegatheeswaran S, Baltatzis M, Jamdar S, Siriwardena AK. Superior mesenteric artery (SMA) resection during pancreatectomy for malignant disease of the pancreas: a systematic review. HPB (Oxford). 2017;19:483–90.
10. Gong Y, Zhang L, He T, et al. Pancreaticoduodenectomy combined with vascular resection and reconstruction for patients with locally advanced pancreatic cancer: a multicenter, retrospective analysis. PLoS One. 2013;8:e70340.

11. Shukla PJ, Barreto SG, Kulkarni A, Nagarajan G, Fingerhut A. Vascular anomalies encountered during pancreatoduodenectomy: do they influence outcomes? Ann Surg Oncol. 2010;17:186–93.
12. Song S-Y, Chung JW, Yin YH, Jae HJ, Kim H-C, Jeon UB, Cho BH, So YH, Park JH. Celiac axis and common hepatic artery variations in 5002 patients: systematic analysis with spiral CT and DSA. Radiology. 2010;255:278–88.
13. Yang SH, Yin YH, Jang J-Y, Lee SE, Chung JW, Suh K-S, Lee KU, Kim S-W. Assessment of hepatic arterial anatomy in keeping with preservation of the vasculature while performing pancreatoduodenectomy: an opinion. World J Surg. 2007;31:2384–91.
14. Asano T, Nakamura T, Noji T, et al. Outcome of concomitant resection of the replaced right hepatic artery in pancreaticoduodenectomy without reconstruction. Langenbecks Arch Surg. 2018;403:195–202.
15. Yamamoto M, Zaima M, Yamamoto H, Harada H, Kawamura J, Yamada M, Yazawa T, Kawasoe J. Liver necrosis shortly after pancreaticoduodenectomy with resection of the replaced left hepatic artery. World J Surg Oncol. 2017;15:77.
16. Hassan R, Ibraheem T, Taha A, Fadel B, Zidan A. Common hepatic artery thrombosis after iatrogenic injury in pancreaticodudenectomy operation, unexpected course. Int J Surg Case Rep. 2016;25:83–5.
17. Yekebas EF, Wolfram L, Cataldegirmen G, et al. Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Ann Surg. 2007;246:269–80.
18. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142:20–5.
19. Correa-Gallego C, Brennan MF, D'Angelica MI, DeMatteo RP, Fong Y, Kingham TP, Jarnagin WR, Allen PJ. Contemporary experience with postpancreatectomy hemorrhage: results of 1,122 patients resected between 2006 and 2011. J Am Coll Surg. 2012;215:616–21.
20. Asari S, Matsumoto I, Toyama H, Yamaguchi M, Okada T, Shinzeki M, Goto T, Ajiki T, Fukumoto T, Ku Y. Recommendation of treatment strategy for postpancreatectomy hemorrhage: lessons from a single-center experience in 35 patients. Pancreatology. 2016;16:454–63.
21. Floortje van Oosten A, Smits FJ, van den Heuvel DAF, van Santvoort HC, Molenaar IQ. Diagnosis and management of postpancreatectomy hemorrhage: a systematic review and meta-analysis. HPB (Oxford). 2019;21:953–61.
22. Kadaba R, Bowers K, Khorsandi S, Hutchins R, Abraham A, Sarker S-J, Bhattacharya S, Kocher H. Complications of biliary-enteric anastomoses. Annals. 2016;99:210–5.
23. Smoot RL, Christein JD, Farnell MB. Durability of portal venous reconstruction following resection during pancreaticoduodenectomy. J Gastrointest Surg. 2006;10:1371–5.
24. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg. 2004;8:935–49; discussion 949–50.
25. Bach AM, Hann LE, Brown KT, Getrajdman GI, Herman SK, Fong Y, Blumgart LH. Portal vein evaluation with US: comparison to angiography combined with CT arterial portography. Radiology. 1996;201:149–54.
26. Tessler FN, Gehring BJ, Gomes AS, Perrella RR, Ragavendra N, Busuttil RW, Grant EG. Diagnosis of portal vein thrombosis: value of color Doppler imaging. AJR Am J Roentgenol. 1991;157:293–6.
27. Condat B, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. Hepatology. 2000;32:466–70.
28. Cho CW, Park YJ, Kim Y-W, Choi SH, Heo JS, Choi DW, Kim D-I. Follow-up results of acute portal and splenic vein thrombosis with or without anticoagulation therapy after hepatobiliary and pancreatic surgery. Ann Surg Treat Res. 2015;88:208–14.
29. Hollingshead M, Burke CT, Mauro MA, Weeks SM, Dixon RG, Jaques PF. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. J Vasc Interv Radiol. 2005;16:651–61.

30. Zyromski NJ, Howard TJ. Acute superior mesenteric-portal vein thrombosis after pancreaticoduodenectomy: treatment by operative thrombectomy. Surgery. 2008;143:566–7.
31. Diehl DL, Blansfield JA. Symptomatic retained prophylactic pancreatic stents. Surgery. 2013;153:881–2.
32. Levy MJ, Chari S, Adler DG, Clain JE, Gostout CJ, Harewood GC, Pearson RK, Petersen BT, Sarr MG, Farnell MB. Complications of temporary pancreatic stent insertion for pancreaticojejunal anastomosis during pancreaticoduodenectomy. Gastrointest Endosc. 2004;59:719–24.
33. Sachs TE, Pratt WB, Kent TS, Callery MP, Vollmer CM. The pancreaticojejunal anastomotic stent: friend or foe? Surgery. 2013;153:651–62.
34. Biffl WL, Moore EE. Pancreaticojejunal stent migration resulting in "bezoar ileus". Am J Surg. 2000;180:115–6.
35. Ortega PM, Zozaya-Larequi G, Arredondo J, Martí-Cruchaga P, Bellver M, Sánchez-Justicia C, Rotellar F, Pardo F. Distal migration of a transanastomotic pancreatic stent resulting in bowel perforation 19 years after pancreatoduodenectomy: report of a case. Surg Today. 2015;45:374–7.
36. Mari G, Costanzi A, Monzio N, Miranda A, Rigamonti L, Crippa J, Sartori P, Maggioni D. Small bowel perforation caused by pancreaticojejunal anastomotic stent migration after pancreaticoduodenectomy for periampullary carcinoma. JOP. 2015;16:185–8.
37. Rezvani M, O'Moore PV, Pezzi CM. Late pancreaticojejunostomy stent migration and hepatic abscess after Whipple procedure. J Surg Educ. 2007;64:220–3.
38. Ansorge C, Regner S, Segersvärd R, Strömmer L. Early intraperitoneal metabolic changes and protease activation as indicators of pancreatic fistula after pancreaticoduodenectomy. Br J Surg. 2012;99:104–11.
39. Hiyoshi M, Chijiiwa K, Fujii Y, Imamura N, Nagano M, Ohuchida J. Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic fistula after pancreaticoduodenectomy. World J Surg. 2013;37:2436–42.
40. Nentwich MF, El Gammal AT, Lemcke T, et al. Salvage completion pancreatectomies as damage control for post-pancreatic surgery complications: a single-center retrospective analysis. World J Surg. 2015;39:1550–6.
41. Palani Velu LK, Chandrabalan VV, Jabbar S, McMillan DC, McKay CJ, Carter CR, Jamieson NB, Dickson EJ. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. HPB (Oxford). 2014;16:610–9.
42. Dalla Valle R, De Bellis M, Pedrazzi G, Lamecchi L, Bianchi G, Pellegrino C, Iaria M. Can early serum lipase measurement be routinely implemented to rule out clinically significant pancreatic fistula after pancreaticoduodenectomy? Int J Surg. 2015;21(Suppl 1):S50–4.
43. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. HPB (Oxford). 2016;18:642–51.
44. Malgras B, Duron S, Gaujoux S, Dokmak S, Aussilhou B, Rebours V, Palazzo M, Belghiti J, Sauvanet A. Early biliary complications following pancreaticoduodenectomy: prevalence and risk factors. HPB (Oxford). 2016;18:367–74.
45. Herzog T, Belyaev O, Hessam S, Uhl W, Chromik AM. Management of isolated bile leaks after pancreatic resections. J Investig Surg. 2014;27:273–81.
46. Andrianello S, Marchegiani G, Malleo G, Pollini T, Bonamini D, Salvia R, Bassi C, Landoni L. Biliary fistula after pancreaticoduodenectomy: data from 1618 consecutive pancreaticoduodenectomies. HPB (Oxford). 2017;19:264–9.
47. Zhou Y, Wang W, Shi Y, Lu X, Zhan Q, Chen H, Deng X, Peng C, Shen B. Substantial atherosclerotic celiac axis stenosis is a new risk factor for biliary fistula after pancreaticoduodenectomy. Int J Surg. 2018;49:62–7.
48. House MG, Cameron JL, Schulick RD, Campbell KA, Sauter PK, Coleman J, Lillemoe KD, Yeo CJ. Incidence and outcome of biliary strictures after pancreaticoduodenectomy. Ann Surg. 2006;243:571–8.
49. Javed AA, Jones GF, Mirza MB, et al. Biliary anastomotic strictures after pancreaticoduodenectomy: an underappreciated complication. HPB. 2018;20:S50.

50. Katabathina VS, Dasyam AK, Dasyam N, Hosseinzadeh K. Adult bile duct strictures: role of MR imaging and MR cholangiopancreatography in characterization. Radiographics. 2014;34:565–86.
51. Thomas S, Jahangir K. Noninvasive imaging of the biliary system relevant to percutaneous interventions. Semin Intervent Radiol. 2016;33:277–82.
52. Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. Pancreatology. 2011;11:268–76.
53. Ferrara MJ, Lohse C, Kudva YC, et al. Immediate post-resection diabetes mellitus after pancreaticoduodenectomy: incidence and risk factors. HPB (Oxford). 2013;15:170–4.
54. Ishikawa O, Ohigashi H, Eguchi H, et al. Long-term follow-up of glucose tolerance function after pancreaticoduodenectomy: comparison between pancreaticogastrostomy and pancreaticojejunostomy. Surgery. 2004;136:617–23.
55. Litwin J, Dobrowolski S, Orłowska-Kunikowska E, Sledziński Z. Changes in glucose metabolism after Kausch-Whipple pancreatectomy in pancreatic cancer and chronic pancreatitis patients. Pancreas. 2008;36:26–30.
56. Kusakabe J, Anderson B, Liu J, et al. Long-term endocrine and exocrine insufficiency after pancreatectomy. J Gastrointest Surg. 2019;23:1604–13.
57. Rahier J, Goebbels RM, Henquin JC. Cellular composition of the human diabetic pancreas. Diabetologia. 1983;24:366–71.
58. Amano H, Takada T, Ammori BJ, et al. Pancreatic duct patency after pancreaticogastrostomy: long-term follow-up study. Hepatogastroenterology. 1998;45:2382–7.
59. Balcom JH, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg. 2001;136:391–8.
60. Reid-Lombardo KM, Ramos-De la Medina A, Thomsen K, Harmsen WS, Farnell MB. Long-term anastomotic complications after pancreaticoduodenectomy for benign diseases. J Gastrointest Surg. 2007;11:1704–11.
61. Demirjian AN, Kent TS, Callery MP, Vollmer CM. The inconsistent nature of symptomatic pancreatico-jejunostomy anastomotic strictures. HPB (Oxford). 2010;12:482–7.
62. Samejima Peternelli N, Wajsfeld T, Henrique Yazawa Santos F, Schmidt de Azevedo O, Altenfelder Silva R, Monteiro Pacheco Junior A. Postoperative complications of Beger procedure. Case Rep Surg. 2015;2015:970785.
63. Ghazanfar MA, Soonawalla Z, Silva MA, Reddy S. Management of pancreaticojejunal strictures after pancreaticoduodenectomy: clinical experience and review of literature. ANZ J Surg. 2018;88:626–9.
64. Prince JM, Fan J, Misra S. Clinical suspicion is key: an unusual presentation of septic arthritis after distal pancreatectomy. J Surg Case Rep. 2019;2019:rjz203.
65. Odufalu F-D, Zubairu J, Silverman W. Bronchobiliary fistula: a rare complication after pancreaticoduodenectomy. BMJ Case Rep. 2018; https://doi.org/10.1136/bcr-2017-221895.
66. Burke CT, Park J. Portal vein pseudoaneurysm with portoenteric fistula: an unusual cause for massive gastrointestinal hemorrhage. Semin Intervent Radiol. 2007;24:341–5.
67. Pansini G, Pascale G, Pigato I, Malvicini E, Andreotti D, Caruso A, Stano R, Occhionorelli S. A rare diaphragmatic hernia with a delayed presentation of intestinal symptoms following spleno-distal pancreatectomy: a case report. J Surg Case Rep. 2017, 2017:rjx135.
68. Bartoli M, Baiocchi GL, Portolani N, Giulini SM. Refractory hepatic lymphorrhea after total pancreatectomy. Case report and literature review of this uncommon complication. Int J Surg Case Rep. 2015;16:134–6.
69. Robinson K, Rajebi MR, Zimmerman N, Zeinati C. Post-pancreaticoduodenectomy hemorrhage of unusual origin: treatment with endovascular embolization and the value of preoperative CT angiography. J Radiol Case Rep. 2013;7:29–36.
70. Welsch T, Hallscheidt P, Schmidt J, Steinhardt HJ, Büchler MW, Sido B. Management of a rare case of fulminant hemobilia due to arteriobiliary fistula following total pancreatectomy. J Gastroenterol. 2006;41:1116–9.

Part IX
Outcomes

Chapter 71
Quality Metrics and Performance Evaluation in Pancreatic Surgery

Kjetil Søreide, Sheraz Yaqub, Zhi Ven Fong, and Motaz Qadan

Take Home Messages

- Pancreatic surgery is associated with improving but substantial morbidity and a wide array of quality metrics have been adopted across the literature.
- Overall complications may serve as a holistic quality metric, but may under-capture cumulative complications that dictate mortality rates.
- Textbook outcomes, failure-to-rescue, and benchmarking are novel tools used to assess quality, but all possess limitations that readers should be cognizant of.

Pearls and Pitfalls

- A wide variety of quality metrics for pancreatic surgery exist in the literature, each with its own limitations.
- Most quality metrics are not patient-centered, with a paucity of emphasis on patient-reported outcomes.
- There has been no consensus on the optimal quality metric that should be adopted and standardized for benchmarking across institutions.

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Future Perspectives
- With advances in electronic medical records that can facilitate data input and tracking, institutions should engage in routine measurement of patient-reported outcomes for incorporation into existing quality metrics.

71.1 Introduction

Pancreatic surgery has historically been a high-risk, complex operation with considerable morbidity. However, the operation has become safer in recent years, likely secondary to improvements in critical care, endoscopic and interventional techniques, and increased regionalization of the care of patients who require pancreatectomy [1–3]. Of all complex surgical procedures, pancreatic surgery most apparently illustrates the volume-outcome relationship and exhibits the biggest differential in mortality rates between high and low volume centers [1]. However, simple volume-metrics are insufficient to gauge quality, and several other modes of performance evaluation have been proposed over the past decade.

The definition of procedure-specific complications in pancreatic surgery has improved over the past decade through consensus work and collaborative studies. Much work has been dedicated to the most common complications, their classification, and best management options. In this chapter, we aim to more broadly review current quality metrics that are being used in pancreatic surgery, with an emphasis on their strengths and limitations of each, as well as propose future directions in this arena.

71.2 Traditional Reporting of Complications

Reporting outcomes after complex surgery may be difficult, as there are many aspects to consider with several outcome metrics that can be potentially used as performance indicators. In any given treatment phase of the patient's care, there may be procedure specific as well as associated medical complications that can impact the recovery trajectory (Fig. 71.1). Some scoring systems only capture the most severe complication and/or outcome and hence fail to consider the course of events that cumulatively may lead to an unfavorable outcome. Also, variation in how outcomes are measured (e.g. specified time-periods for inclusion of event) may vary, which makes comparison across institutions, regions, countries or health care systems difficult.

71.2.1 Procedure-Specific Complications

For pancreatic surgery, there are several complications specific to the operation itself that are common but occur with varying severity. Most important among these are post-operative pancreatic fistula, [4] post-pancreatectomy hemorrhage, [5]

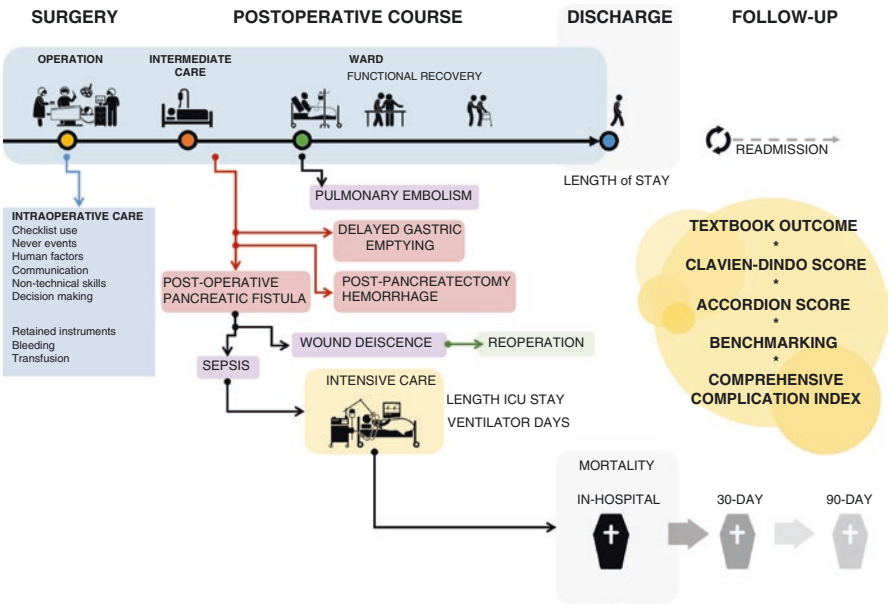

Fig. 71.1 Complexities in the patient journey in assessing performance and outcomes. Depicted are the several phases of a patient's clinical care, going from intraoperative events that may have spillover effects on the post-operative course. An uneventful recovery may achieve a "textbook outcome". As illustrated, if one complication were to occur, several others may follow. Some complication systems only capture the worst, while others try to accumulate these in cumulative scores to more accurately depict its burden. Some complications may be procedure specific (e.g. marked in red), while others are more general (e.g. marked in purple). For details, please see main body of text (illustration KSoreide©2020)

delayed gastric emptying [6] and chyle leak [7]—all of which have been defined and graded through consensus work by the International Study Group of Pancreatic Surgery (ISGPS), and are discussed below.

71.2.2 Length of Hospital Stay

Length of hospital stay is a commonly utilized metric in the past, where longer stay was typically associated with complications and need for continued care until safe discharge could occur. However, this metric is unreliable as it varies substantially between hospital payer systems, country-specific practices, and may be influenced by many factors unrelated to clinical care. This metric also does not capture subsequent admission to secondary units, recovery facility, or readmission-related hospital days. To that point, in a study using administrative data of hospital episodes for all digestive tract resections in a universal health care system over a 5-year period, the authors found considerable differences in length of stay depending on the method used to calculate hospital stays [8]. An "aggregated length of stay", which

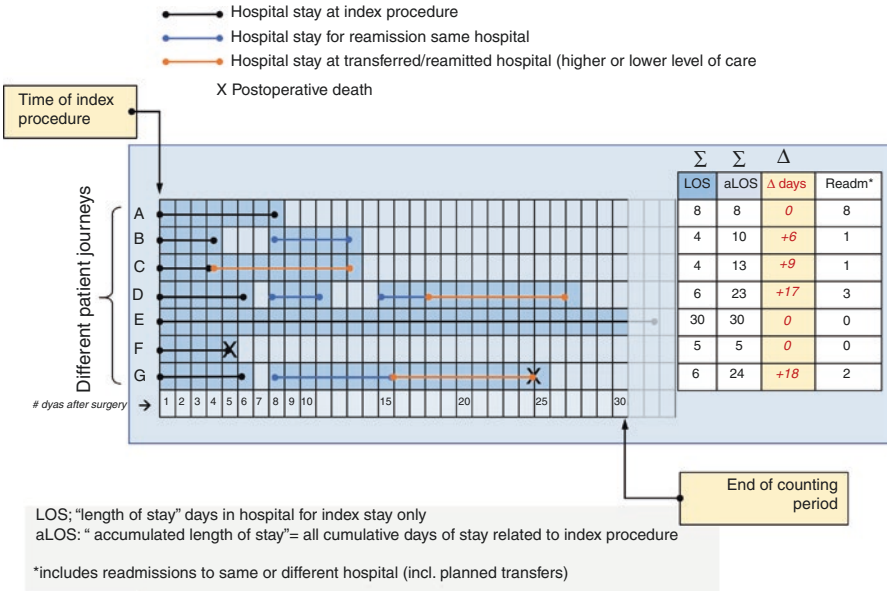

Fig. 71.2 Variations in counting length of stay. Depicted are various patient phases of care (A–G) and different methodologies of counting the hospital length of stay, e.g. only using the index stay as a metric or, including all stays, including transfer and readmission days. It is also worth noting that depending on the time-period set for endpoint capture, certain hospital and readmission days and related deaths would have been missed, such as that depicted in patient journey 'E'. (KSoreide©2020)

is the total length of all accumulated days in the hospital was proposed, which may better reflect the utilization of hospital resources between institutions (Fig. 71.2).

When aLoS was investigated [8], the median index procedure hospital stay for pancreatoduodenectomies was 9 days, but increased to a median of 14 days when "aggregated length of stay (aLoS)" was utilized, having added the days for transfers to other facilities (56.8% of patients) and for readmissions (12.4% of patients). Notably, for pancreatoduodenectomy, about one-third of the accumulated hospital stay was caused by days added beyond the index stay, which may more accurately reflect the use of hospital resources within a health care system, rather than just for the index hospitalization. Similar patterns where found for distal pancreatectomies [9, 10], with less prominent differences for laparoscopic distal resections.

71.2.3 Readmissions

Throughout the 2010s, readmission had been scrutinized as a potential quality metric for pancreatic surgery given its adoption by the Center for Medicare and Medicaid services in the United States as a metric that dictated reimbursements for targeted medical conditions such as pneumonia and heart failure [11, 12]. It

ultimately proved to be a poor quality metric for pancreatic surgery given that a significant proportion of its complications occur later in the course of recovery [13, 14]. If readmissions were to be used as a quality indicator, it might dangerously discourage providers to appropriately admit patients for rescue interventions. Separately, in a study of almost ten million Medicare patients covering 12 surgical procedures, readmission to the index hospital was associated with a 26% lower risk of 90-day mortality than readmission to a non-index hospital, with the most pronounced effect observed following pancreatectomy [15]. As such, a more reliable metric may therefore incorporate intent of patients to undergo rescue interventions at index facilities (i.e. patient 'ownership), although this may prove to be impractical given that most patients travel to referral centers for their care and do not necessarily reside near the index hospital of record [16].

71.2.4 In-Hospital Mortality After Surgery

In-hospital mortality has been used as a metric to gauge performance, but discounts the importance of its incidence after hospital discharge. In a nationwide cohort from Norway, the 30-day mortality was 2%, but doubled to 4% when assessed at 90-days [17]. In a separate study of 24,798 patients in North America, the 30-day mortality rate after pancreatectomy was 2.5%, but rose to 7.1% when 90-day mortality was measured [18]. While it may require more resources, this emphasizes the need for longitudinal quality assessment beyond historic 30- and 90-day time intervals, while balancing perioperative outcomes with oncologic outcomes that start to appear shortly thereafter.

Box 71.1 Clavien-Dindo Score [19]

Degree	Definition
I	Every deviation from normal postoperative course without the necessity for drug treatment or a surgical, endoscopic or radiological intervention. Permissible therapeutic measures: drugs from the substance classes antiemetics, antipyretics, analgesics, diuretics; electrolyte substitution and physiotherapy. Surgical treatment of wound infections at the bedside
II	Drug treatment in excess of the pharmacological measures listed under degree I. Blood transfusions and parenteral nutrition
III	Necessity for surgical, endoscopic or radiological intervention **IIIa**: Intervention without general anaesthesia **IIIb**: Intervention with general anaesthesia
IV	Life-threatening complications leading to transfer to an intermediate care or intensive care unit **IVa** Dysfunction of an organ system (including the necessity for temporary dialysis) **IVb** Multiorgan dysfunction
V	Death, any cause

Box 71.2 Accordion severity grading system[20] (expanded classification)

1. Mild complication
Requires only minor invasive procedures that can be done at the bedside such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
2. Moderate complication
Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included
3. Severe: invasive procedure without general anesthesia
Requires management by an endoscopic, interventional procedure or re-operation[a] without general anesthesia
4. Severe: operation under general anesthesia
Requires management by an operation under general anesthesia
5. Severe: organ system failure[b]
6. Death
Postoperative death

[a]An example would be a wound re-exploration under conscious sedation and/or local anesthetic

[b]Such complications would normally be managed in an increased acuity setting, but in some cases patients with complications of lower severity might also be admitted to an ICU. Reproduced as presented in Strasberg et al. [20]

71.3 Grading of Complications After Surgery

While complications are common after pancreatic surgery, they vary significantly in severity and their impact on mortality. Two of the most frequently utilized grading systems of complications are the Clavien-Dindo and the Accordion score (Boxes 71.1 and 71.2).

71.4 Comprehensive Complication Index

Using complications as a quality metric is not straight forward and one needs to keep in mind that the quality metrics are only as good as its measurement, its frequency and its reliability. Several complications and adverse events may be flawed as outcome metrics, as they are rare events (e.g. perioperative mortality) or unreliably measured (e.g. venous thromboembolism is a rare clinical event, depends on

symptoms or definitions and intensity of imaging done for detection, and may be either asymptomatic or a clinically relevant event). A good example of this in pancreatic surgery may be the variation between studies reporting on post-operative pancreatic fistulae and the associated risk factors and outcomes [21].

One distinct limitation associated with both the Clavien-Dindo and the Accordion score is the inability to quantify the sum of cumulative complications because these systems derive the score from the most severe complication associated with the operation. In an effort to address this, a comprehensive complication index (CCI) was proposed [22]. The CCI is calculated as the sum of all complications that are weighted for their severity (multiplication of the median reference values from patients and physicians). The final formula yields a continuous scale to rank the severity of any combination of complications from 0 to 100 in a single patient. When assessed against the Clavien-Dindo score, CCI was more strongly associated with length of hospital stay than the Clavien-Dindo score. For prolonged hospital stays (≥30 days), only the CCI showed a moderate correlation, while the Clavien-Dindo score did not, suggesting its superiority in measuring surgical quality [23]. Additionally, given that it is a continuous variable, it has been shown to significantly decrease sample size requirements for clinical trials and serves as an appealing endpoint for future trials given its superior sensitivity in measuring surgical morbidity [24].

71.5 Measuring Quality of Care Beyond Traditional Metrics

The previously mentioned traditional outcome metrics such as length of hospital stay and 30-day mortality do not sufficiently gauge institution performances uniformly across various regions and health care systems and don't provide a complete root-cause analysis. Given that, there have been recent efforts aimed at developing more robust performance metrics, of which some are discussed here in relation to pancreatic surgery.

71.5.1 Failure to Rescue

Given the known variation in mortality rates across hospitals performing pancreatectomy, there has been interest in determining if this was due to the differences in complication rates or the ability to rescue patients from complications. Failure to rescue is a quality metric that attempts to address this issue. Several proposed definitions exist, but the most commonly used definition has been the rate of 90-day mortality among patients with major complications [25]. A high failure to rescue rate may indicate the lack of timely recognition and management of a complication, and in turn, poor eventual outcomes [25–28]. This is particularly important in pancreatic surgery, where early recognition and intervention by skilled endoscopists and interventional radiologists is critical in rescuing patients from potentially fatal

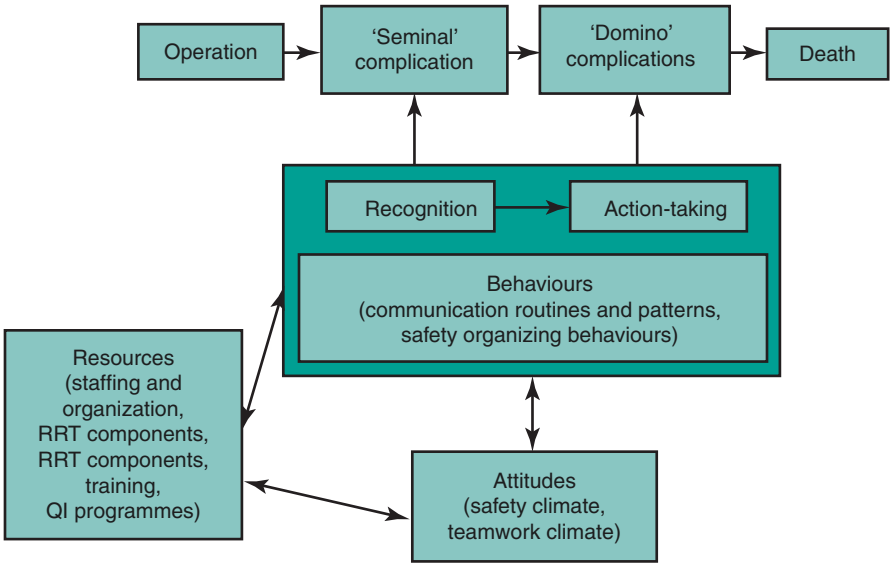

Fig. 71.3 Importance of structure and team-work to avoid failure-to-rescue. Conceptual model of the organizational dynamics affecting complication rescue. RRT rapid response team, QI quality improvement. (Reproduced with permission from Br J Surg, [29] Wiley © 2016)

complications such as gastroduodenal artery pseudoaneurysm bleeding. Not surprisingly, patients who were older and more frail were more susceptible to failure-to-rescue, highlighting the importance of heightened awareness and early recognition of complications in this population [29–31]. At the hospital level, lower nurse-to-patient ratios, fewer intensive care bed availability, understaffing, hierarchal culture and lack of junior staff support were associated with higher failure to rescue rates [27, 32]. This metric provides insight to potentially actionable avenues that could improve rescue rates, such as improved communication within and between teams and safety culture of hospitals (Fig. 71.3).

71.5.2 Textbook Outcomes

While all the aforementioned quality indicators such as morbidity, readmission and mortality rate are inter-related to a certain extent, these may not holistically capture the quality of care provided throughout the hospital course [33]. As such, a composite measure termed 'textbook outcomes' has recently been coined with the purpose of providing a more reliable measure of overall quality [34]. When the metric was first proposed, textbook outcome was defined as the absence of complication, prolonged length of stay (>75th percentile), readmission, or death. In a study of 8035 Medicare patients undergoing pancreatectomy in the United States, the composite outcome was achieved in 44.1% of patients, and is more

likely to be achieved if patients underwent pancreatectomy in a major teaching hospital or at high-volume (≥20 resections per year) centers [35]. For patients with pancreatic cancer, the outcome was more likely to be achieved at dedicated cancer centers [36].

In an attempt to achieve consensus on its definition, the Dutch Pancreatic Cancer Group conducted a survey of 24 international experts (Box 71.3) in pancreatic surgery and identified predictors of achieving the outcome using the Dutch Pancreatic Cancer Audit [37]. Importantly, and in contrast to other specialties, textbook outcome in pancreatic surgery did not include any pathological parameters. The experts agreed that in contrast to other cancers, margin

Box 71.3 Proposed Definition of 'Textbook Outcome' in Pancreatic Surgery

Defined as absence of
• Postoperative pancreatic fistula (ISGPS grade B/C)
• Bile leak
• Post-pancreatectomy haemorrhage
• Severe complication (Clavien Dindo grade ≥ III)
• In-hospital mortality

Based on definitions in the Dutch Pancreatic Cancer Audit [37]

status in pancreatic cancer more frequently reflected the extent of disease biology than in other resectable solid tumors. Of 3341 patients, textbook outcome was successfully achieved in 60.3% of patients. In pancreatoduodenectomy, textbook outcome was predicted by a dilated pancreatic duct (≥3 mm) and pancreatic adenocarcinoma as indication for the operation. ASA class 3 was associated with the risk of not achieving a textbook outcome. In patients undergoing distal pancreatectomy, female gender and the absence of neoadjuvant treatment predicted textbook outcome. In the Netherlands, 18 out of the 20 centers performing pancreatic surgery perform ≥20 resections a year, with 5 centers performing ≥40 operations per year. Despite this high proportion of 'high-volume' centers, there was considerable variation in textbook outcome rates between institutions even after adjusting for case-mix, which reiterates the need for quality assurance programs and audit.

As a metric, textbook outcome has its inherent limitations. Length of stay is a common barrier to patients achieving textbook outcome [38]. However, inclusion of length of stay in textbook outcomes is problematic since there are cultural, organizational and economic factors that heavily influence length of stay between countries. For example, Asian centers frequently suffer from prolonged hospitalization periods compared with their European and US counterparts. In one analysis, when

length of stay was removed from the textbook outcome, Eastern hospitals went from exhibiting consistently lower rates of textbook outcome than Western centers to consistently higher rates [39]. Presently, the consensus definition as published by the Dutch group excludes length of hospital stay as a criterion for textbook outcome because of low agreement between experts. Whether this will be adopted widely is yet to be determined [40]. Additionally, because this is a composite metric, it doesn't provide any granularity to the root cause of low attainment rates, and needs to be deconstructed to inform quality improvement purposes.

71.5.3 Benchmarking in Surgery

Benchmarking is defined as comparative assessment of high-level performance and is adopted from economic evaluation studies [41]. Benchmarking facilitates the understanding of processes by which performance can be compared, and thus improved. Rather than comparing averages across a spectrum, benchmarking addresses the top tier performance (e.g. the 75th percentile) and sets it as a standard to reach. As the benchmark represents the best possible outcome, the gap between benchmark and performance reflects the theoretical potential to improve. A suggested 10-step process (Box 71.4) to arrive at benchmark for a surgical procedure has been proposed [41] (Fig. 71.4).

Box 71.4 Ten steps to develop a benchmark[41]

1. **Intervention:** Select intervention desired to benchmark
2. **Patients:** Specify requirements (benchmark criteria) of patients to represent the lowest risk for complications
3. **Outcome**: Define specific key indicators of outcome (benchmarks) and how they can be measured
4. **Centres**: Find eligible centres for benchmark determination
5. **Number**: Number of centres needed:
6. **Contact**: Research leaders contact candidate centres for collaboration inquiry
7. **Extract**: Extract the predefined patients with the lowest expected postoperative morbidity of each centre
8. **Collect**: Collect data (patient characteristics, benchmark values) for the chosen intervention of each included centre
9. **Calculate**: Calculate the median (continuous benchmark values) or the proportion (binary benchmark values) of each benchmark value individually for each centre
10. **Benchmark**: Compute the 75th percentile by taking each centre's median to determine the benchmark value

Reproduced with permission from [41]

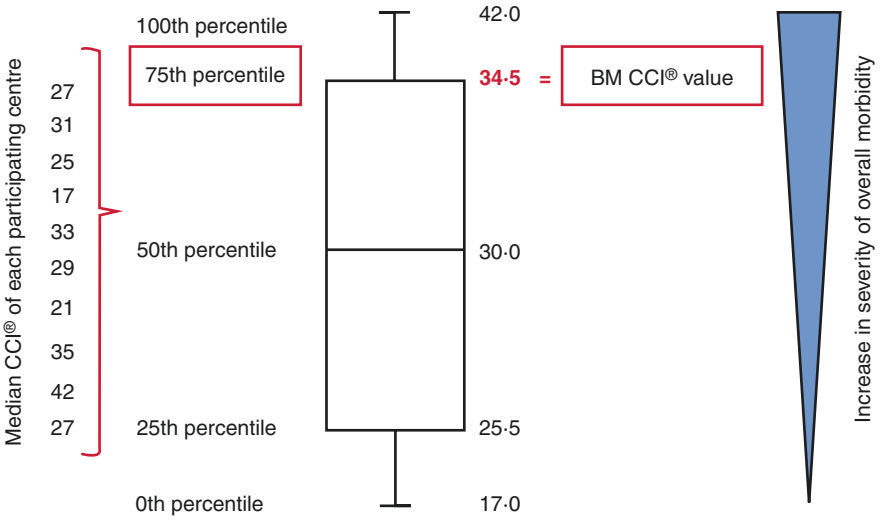

Fig. 71.4 Example of calculation for benchmarking. Calculation of the Comprehensive Complication Index (CCI®) benchmark (BM) value from the median CCI® of each participating centre. The number of benchmark procedures per centre (number size) does not influence the result. The higher the CCI® value, the greater the severity of overall morbidity. Within this cohort of lowest-risk patients, the cut-off at the 75th percentile to determine the benchmark value excludes the 25% of patients with the highest overall morbidity. Reproduced from Staiger RD, et al. Improving surgical outcomes through benchmarking. Br J Surg. 2019 Jan;106(1):59–64 with permission from Wiley ©2019

Box 71.5 Select benchmark cut-off values (eight of a total 20 reported)

- Operation duration: ≤7.5 h
- Blood transfusions: ≤23%
- Hospital stay: ≤15 days
- POPF grade C rate: ≤5%
- CCI score: ≤20.9
- In-hospital mortality: ≤1.6%
- Failure to rescue rate: ≤9%
- Readmission rate: ≤21%

A benchmark may be used within a hospital or between hospitals with defined actions needed to take in order to close a gap between outcomes, and, as such, potentially lead to an improved performance. Currently, only one large, multicentre study has reported on benchmark values in pancreatic surgery [42]. Based on a cohort derived from 23 referral centres consisting of over 6186 pancreatoduodenectomies, a total of 2375 (38%) low-risk patients were deemed eligible for benchmark analysis. The investigators arrived at benchmark cut-off values for 20 endpoints, of which selected numbers are presented in Box 71.5.

Of note, huge variation between the selected centers chosen for the benchmark outcomes were found, as were variation in center volume and case-mix. One can argue that some of the benchmark values chosen, such as R1-rate and number of harvested lymph nodes, are poor metrics for gauging performance. However, the investigators proposed that such metrics may be used to compare differences in performance between centers, gauge the outcome for introducing new technology (e.g. minimal-invasive pancreatic surgery) and identify patients who fall outside the benchmark for discussion at quality improvement meetings. Whether this form of quality metric and performance evaluation will supersede alternative outcomes, including textbook outcomes, remains to be seen [43].

71.6 Future Directions

To date, most quality metrics proposed and adopted by national registries do not incorporate patient perspectives, and consequently are not patient-centric. In studies assessing long-term quality of life scores in patients who have undergone pancreatic resection, patients often struggle with gastrointestinal dysfunction, and up to 50% and 15% required pancreatic enzyme replacement and insulin therapy, respectively [44–47]. While these published data can better inform shared decision making in the preoperative setting, they need to be better tracked longitudinally to identify potential actionable domains.

The increased sophistication of modern day electronic medical health records can facilitate input and longitudinal tracking of patient-reported outcomes [48], and should be an avenue worth investing in for hospitals performing complex operations such as pancreatic resections. As our patients live longer with better systemic therapy and safer operations, it is imperative that we start incorporating patient-centered outcomes into quality metrics to more accurately track their wellbeing after their postoperative recovery.

71.7 Conclusion

Pancreatic surgery is a complex operation associated with high morbidity and mortality rates. As we continue to refine the operation and improve perioperative care, its outcomes need to be closely tracked for quality improvement purposes. While there has been a wide array of individual and composite metrics used, they each are associated with their own limitations. Clinicians and academics need to understand the utility of each metric, and be cognizant of each of their specific shortcomings to accurately interpret outcomes published across the literature.

References

1. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med. 2011;364(22):2128–37. https://doi.org/10.1056/NEJMsa1010705.
2. Song Y, Tieniber AD, Roses RE, Fraker DL, Kelz RR, Karakousis GC. National trends in centralization and perioperative outcomes of complex operations for cancer. Surgery. 2019;166(5):800–11. https://doi.org/10.1016/j.surg.2019.03.025.
3. Sheetz KH, Dimick JB, Nathan H. Centralization of high-risk Cancer surgery within existing hospital systems. J Clin Oncol. 2019;37(34):3234–42. https://doi.org/10.1200/jco.18.02035.
4. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017;161(3):584–91. https://doi.org/10.1016/j.surg.2016.11.014.
5. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an international study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20–5. https://doi.org/10.1016/j.surg.2007.02.001.
6. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the international study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761–8. https://doi.org/10.1016/j.surg.2007.05.005.
7. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the international study group on pancreatic surgery. Surgery. 2017;161(2):365–72. https://doi.org/10.1016/j.surg.2016.06.058.
8. Lassen K, Nymo LS, Olsen F, Soreide K. Benchmarking of aggregated length of stay after open and laparoscopic surgery for cancers of the digestive system. BJS Open. 2018;2(4):246–53. https://doi.org/10.1002/bjs5.67.
9. Soreide K, Nymo LS, Kleive D, Olsen F, Lassen K. Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system. Pancreatology. 2019;19(6):880–7. https://doi.org/10.1016/j.pan.2019.07.047.
10. Soreide K, Olsen F, Nymo LS, Kleive D, Lassen K. A nationwide cohort study of resection rates and short-term outcomes in open and laparoscopic distal pancreatectomy. HPB (Oxford). 2019;21(6):669–78. https://doi.org/10.1016/j.hpb.2018.10.006.
11. Desai NR, Ross JS, Kwon JY, Herrin J, Dharmarajan K, Bernheim SM, et al. Association between hospital penalty status under the hospital readmission reduction program and readmission rates for target and nontarget conditions. JAMA. 2016;316(24):2647–56. https://doi.org/10.1001/jama.2016.18533.
12. Ryan AM, Krinsky S, Adler-Milstein J, Damberg CL, Maurer KA, Hollingsworth JM. Association between Hospitals' engagement in value-based reforms and readmission reduction in the hospital readmission reduction program. JAMA Intern Med. 2017;177(6):862–8. https://doi.org/10.1001/jamainternmed.2017.0518.
13. Fong ZV, Ferrone CR, Thayer SP, Wargo JA, Sahora K, Seefeld KJ, et al. Understanding hospital readmissions after pancreaticoduodenectomy: can we prevent them?: a 10-year contemporary experience with 1,173 patients at the Massachusetts General Hospital. J Gastrointest Surg. 2014;18(1):137–44; discussion 44-5. https://doi.org/10.1007/s11605-013-2336-9.
14. Sadot E, Brennan MF, Lee SY, Allen PJ, Gonen M, Groeger JS, et al. Readmission after pancreatic resection: causes and causality pattern. Ann Surg Oncol. 2014;21(13):4342–50. https://doi.org/10.1245/s10434-014-3841-0.
15. Brooke BS, Goodney PP, Kraiss LW, Gottlieb DJ, Samore MH, Finlayson SR. Readmission destination and risk of mortality after major surgery: an observational cohort study. Lancet. 2015;386(9996):884–95. https://doi.org/10.1016/s0140-6736(15)60087-3.

16. Fong ZV, Loehrer AP, Fernandez-Del Castillo C, Bababekov YJ, Jin G, Ferrone CR, et al. Potential impact of a volume pledge on spatial access: a population-level analysis of patients undergoing pancreatectomy. Surgery. 2017;162(2):203–10. https://doi.org/10.1016/j.surg.2017.03.010.
17. Nymo LS, Soreide K, Kleive D, Olsen F, Lassen K. The effect of centralization on short term outcomes of pancreatoduodenectomy in a universal health care system. HPB (Oxford). 2019;21(3):319–27. https://doi.org/10.1016/j.hpb.2018.08.011.
18. Wegner RE, Verma V, Hasan S, Schiffman S, Thakkar S, Horne ZD, et al. Incidence and risk factors for post-operative mortality, hospitalization, and readmission rates following pancreatic cancer resection. J Gastrointest Oncol. 2019;10(6):1080–93. https://doi.org/10.21037/jgo.2019.09.01.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
20. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg. 2009;250(2):177–86. https://doi.org/10.1097/SLA.0b013e3181afde41.
21. Søreide K, Healey AJ, Mole DJ, Parks RW. Pre-, peri- and post-operative factors for the development of pancreatic fistula after pancreatic surgery. HPB (Oxford). 2019;21(12):1621–31. https://doi.org/10.1016/j.hpb.2019.06.004.
22. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013;258(1):1–7. https://doi.org/10.1097/SLA.0b013e318296c732.
23. Kim TH, Suh YS, Huh YJ, Son YG, Park JH, Yang JY, et al. The comprehensive complication index (CCI) is a more sensitive complication index than the conventional Clavien-Dindo classification in radical gastric cancer surgery. Gastric Cancer. 2018;21(1):171–81. https://doi.org/10.1007/s10120-017-0728-3.
24. Slankamenac K, Nederlof N, Pessaux P, de Jonge J, Wijnhoven BP, Breitenstein S, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg. 2014;260(5):757–62; discussion 62-3. https://doi.org/10.1097/sla.0000000000000948.
25. El Amrani M, Clement G, Lenne X, Farges O, Delpero JR, Theis D, et al. Failure-to-rescue in patients undergoing pancreatectomy: is hospital volume a standard for quality improvement programs? Nationwide analysis of 12,333 patients. Ann Surg. 2018;268(5):799–807. https://doi.org/10.1097/sla.0000000000002945.
26. Amini N, Spolverato G, Kim Y, Pawlik TM. Trends in hospital volume and failure to rescue for pancreatic surgery. J Gastrointest Surg. 2015;19(9):1581–92. https://doi.org/10.1007/s11605-015-2800-9.
27. van Rijssen LB, Zwart MJ, van Dieren S, de Rooij T, Bonsing BA, Bosscha K, et al. Variation in hospital mortality after pancreatoduodenectomy is related to failure to rescue rather than major complications: a nationwide audit. HPB (Oxford). 2018;20(8):759–67. https://doi.org/10.1016/j.hpb.2018.02.640.
28. Krautz C, Nimptsch U, Weber GF, Mansky T, Grutzmann R. Effect of hospital volume on in-hospital morbidity and mortality following pancreatic surgery in Germany. Ann Surg. 2018;267(3):411–7. https://doi.org/10.1097/sla.0000000000002248.
29. Ghaferi AA, Dimick JB. Importance of teamwork, communication and culture on failure-to-rescue in the elderly. Br J Surg. 2016;103(2):e47–51. https://doi.org/10.1002/bjs.10031.
30. Tamirisa NP, Parmar AD, Vargas GM, Mehta HB, Kilbane EM, Hall BL, et al. Relative contributions of complications and failure to rescue on mortality in older patients undergoing pancreatectomy. Ann Surg. 2016;263(2):385–91. https://doi.org/10.1097/sla.0000000000001093.
31. Gleeson EM, Clarke JR, Morano WF, Shaikh MF, Bowne WB, Pitt HA. Patient-specific predictors of failure to rescue after pancreaticoduodenectomy. HPB (Oxford). 2019;21(3):283–90. https://doi.org/10.1016/j.hpb.2018.07.022.

32. Sheetz KH, Dimick JB, Ghaferi AA. Impact of hospital characteristics on failure to rescue following major surgery. Ann Surg. 2016;263(4):692–7. https://doi.org/10.1097/SLA.0000000000001414.
33. Dimick JB, Staiger DO, Baser O, Birkmeyer JD. Composite measures for predicting surgical mortality in the hospital. Health Aff (Millwood). 2009;28(4):1189–98. https://doi.org/10.1377/hlthaff.28.4.1189.
34. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. JAMA. 2006;295(10):1168–70. https://doi.org/10.1001/jama.295.10.1168.
35. Mehta R, Paredes AZ, Tsilimigras DI, Moro A, Sahara K, Farooq A, et al. Influence of hospital teaching status on the chance to achieve a textbook outcome after hepatopancreatic surgery for cancer among Medicare beneficiaries. Surgery. 2020;168:92–100. https://doi.org/10.1016/j.surg.2020.02.024.
36. Mehta R, Tsilimigras DI, Paredes AZ, Sahara K, Dillhoff M, Cloyd JM, et al. Dedicated cancer centers are more likely to achieve a textbook outcome following hepatopancreatic surgery. Ann Surg Oncol. 2020;27(6):1889–97. https://doi.org/10.1245/s10434-020-08279-y.
37. van Roessel S, Mackay TM, van Dieren S, van der Schelling GP, Nieuwenhuijs VB, Bosscha K, et al. Textbook outcome: nationwide analysis of a novel quality measure in pancreatic surgery. Ann Surg. 2020;271(1):155–62. https://doi.org/10.1097/SLA.0000000000003451.
38. Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, Kolfschoten NE, de Jong PC, Rozema T, et al. Textbook outcome as a composite measure in oesophagogastric cancer surgery. Br J Surg. 2017;104(6):742–50. https://doi.org/10.1002/bjs.10486.
39. Merath K, Chen Q, Bagante F, Alexandrescu S, Marques HP, Aldrighetti L, et al. A multi-institutional international analysis of textbook outcomes among patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma. JAMA Surg. 2019;154(6):e190571. https://doi.org/10.1001/jamasurg.2019.0571.
40. Aiken T, Abbott DE. Textbook oncologic outcome: a promising summary metric of high-quality care, but are we on the same page? J Surg Oncol. 2020;121(6):923–4. https://doi.org/10.1002/jso.25872.
41. Staiger RD, Schwandt H, Puhan MA, Clavien PA. Improving surgical outcomes through benchmarking. Br J Surg. 2019;106(1):59–64. https://doi.org/10.1002/bjs.10976.
42. Sanchez-Velazquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, et al. Benchmarks in pancreatic surgery: a novel tool for unbiased outcome comparisons. Ann Surg. 2019;270(2):211–8. https://doi.org/10.1097/sla.0000000000003223.
43. Pitt HA. Benchmark, textbook or optimal pancreatic surgery? Ann Surg. 2019;270(2):219–20. https://doi.org/10.1097/sla.0000000000003377.
44. Fong ZV, Alvino DM, Castillo CF, Nipp RD, Traeger LN, Ruddy M, et al. Health-related quality of life and functional outcomes in 5-year survivors after pancreaticoduodenectomy. Ann Surg. 2017;266(4):685–92. https://doi.org/10.1097/SLA.0000000000002380.
45. Allen CJ, Yakoub D, Macedo FI, Dosch AR, Brosch J, Dudeja V, et al. Long-term quality of life and gastrointestinal functional outcomes after pancreaticoduodenectomy. Ann Surg. 2018;268(4):657–64. https://doi.org/10.1097/SLA.0000000000002962.
46. Shah KP, Baugh KA, Brubaker LS, Van Buren G II, Villafane-Ferriol N, McElhany AL, et al. Long-term assessment of pancreatic function after pancreatectomy for cystic neoplasms. J Surg Res. 2020;247:547–55. https://doi.org/10.1016/j.jss.2019.09.045.
47. Lim PW, Dinh KH, Sullivan M, Wassef WY, Zivny J, Whalen GF, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. HPB (Oxford). 2016;18(4):360–6. https://doi.org/10.1016/j.hpb.2015.11.003.
48. Hernandez-Boussard T, Tamang S, Blayney D, Brooks J, Shah N. New paradigms for patient-centered outcomes research in electronic medical records: an example of detecting urinary incontinence following prostatectomy. EGEMS. 2016;4(3):1231. https://doi.org/10.13063/2327-9214.1231.

Chapter 72
Surveillance After Surgery for Pancreatic Cancer

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Take Home Messages

- Disease recurrence remains the main cause of mortality in patients who underwent pancreatic cancer resection.
- A combination of elevated serum tumour markers and progressive, suspicious findings on imaging indicates pancreatic cancer recurrence.
- Despite its limitations, CA 19-9 remains the most assessed tumour marker for surveillance purposes.
- CT imaging is the preferred imaging modality for postoperative surveillance; however, PET-CT can be helpful to differentiate between non-specific postoperative changes and local tumour recurrence.
- The optimal surveillance strategy remains a subject of discussion, although a surveillance strategy with 3–6 monthly serum CA 19-9 testing and CT imaging is increasingly recommended.

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Pearls and Pitfalls

- A combination of serial serum tumour marker testing and routine follow-up imaging could aid in the early detection of pancreatic cancer recurrence.
- Advancements in systemic and local ablative therapies have opened the therapeutic framework for treatment of pancreatic cancer recurrence.
- Retrospective studies suggest both survival and quality of life benefits of recurrence-focused surveillance after pancreatic cancer resection.
- Survival and quality of life benefits of early detection and treatment of pancreatic cancer recurrence have yet to be established.
- The optimal method, frequency and duration of surveillance after pancreatic cancer resection remains unclear.
- Recurrence-focused surveillance is increasingly being implemented, although high-quality evidence on this subject is lacking.

Future Perspectives

- Prospective studies are needed to evaluate the true value of early detection and treatment of pancreatic cancer recurrence with regard to survival and quality of life.
- Current research focuses on further development of liquid biopsies for the measurement of circulating tumour cells and DNA as a promising method for detection of disease recurrence during surveillance after pancreatic cancer resection.

72.1 Introduction

Disease recurrence after pancreatic cancer resection remains one of the biggest challenges in pancreatic cancer treatment. Despite the administration of (neo-)adjuvant systemic therapy, almost all patients experience local and/or systemic disease recurrence after sufficient follow-up [1]. The prognosis of patients with pancreatic cancer recurrence remains very poor, with a median post-recurrence survival of only 3–9 months [2, 3]. As limited effective palliative treatment options are available, the value of recurrence-focused surveillance for the early detection and treatment of pancreatic cancer recurrence remains controversial [4, 5].

Recent advancements in pancreatic cancer treatment, however, have resulted in an extended disease-free interval after pancreatic cancer surgery [6]. Adjuvant chemotherapy regimens have been improved and the importance of completing adjuvant treatment is being emphasized [7–9]. Additionally, alternative treatment strategies for localized pancreatic cancer, such as neoadjuvant therapy, are increasingly considered [10–12]. This allows for a better patient selection for surgery, improving the *a priori* prognosis of patients undergoing pancreatic resection. As early disease recurrence in particular is associated with a poor prognosis, a prolonged disease-free interval opens the possibilities for palliative treatment of recurrence [6, 13]. Furthermore, with more effective systemic and locally ablative

treatment options currently available, the therapeutic framework for the treatment of pancreatic cancer recurrence has been expanded [4, 14–16]. Several small, retrospective studies suggest both improvement in survival and quality of life [16–21]. However, prospective studies evaluating these new therapies are lacking. Nevertheless, an increased interest in the early detection and treatment of pancreatic cancer recurrence exists. Standardized surveillance with routine tumour marker testing and imaging after surgery has been suggested for the early detection of disease recurrence. Nonetheless, the optimal method, frequency and duration of postoperative follow-up remains a subject of discussion, with widely varying surveillance strategies being recommended in pancreatic cancer guidelines worldwide [5].

72.2 Current Practice

Pancreatic cancer recurrence is generally diagnosed through a rise in serum tumour markers combined with suspicious, progressive findings on imaging, which is either performed as part of a routine follow-up or clinically indicated (Figs. 72.1 and 72.2). A combination of serial serum tumour marker testing and radiographic imaging with a certain interval could therefore aid in the early detection of disease recurrence. Without standardized diagnostic testing, pancreatic cancer recurrence is usually detected after the manifestation of symptoms, which is associated with a more advanced disease stage [13].

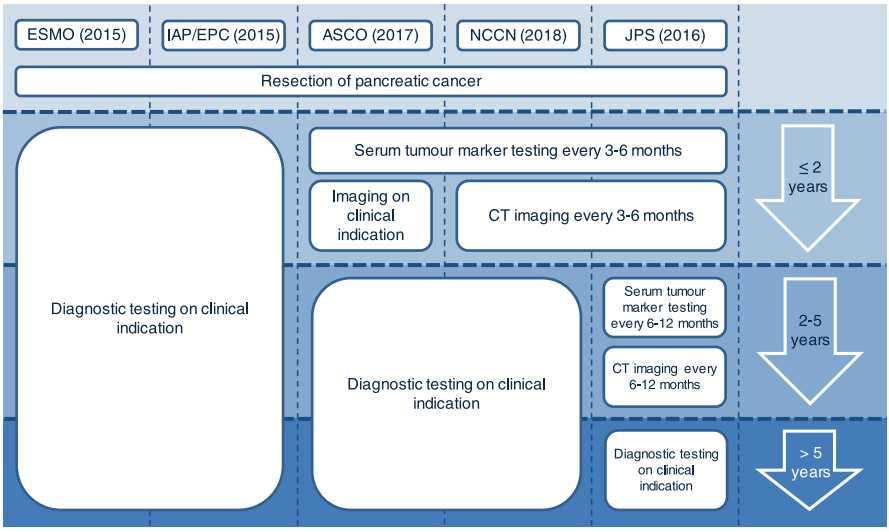

Fig. 72.1 Algorithm for diagnostic testing during the first 5 years after resection of pancreatic ductal adenocarcinoma as recommended by the European Society for Medical Oncology (ESMO), the International Association of Pancreatology/European Pancreatic Club (IAP/EPC), the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Japan Pancreas Society (JPS)

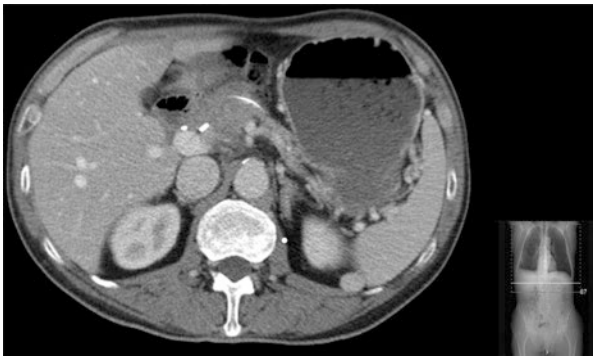

Fig. 72.2 A 70 year old man presented with abdominal pain and weight loss 7 months after pancreatoduodenectomy for a T3N1 R0 pancreatic head tumour. Postoperatively, a symptomatic follow-up approach was applied, without serum tumour marker testing or follow-up imaging, according to the current European guidelines [32]. As the patients' symptoms were suggestive of disease recurrence, a CT scan of thorax and abdomen was clinically indicated, which showed isolated local pancreatic cancer recurrence. Since the patient experienced significant toxicity during adjuvant systemic treatment with gemcitabine chemotherapy, no palliative chemotherapy was started. However, local ablative therapy with stereotactic body radiation therapy (5 × 7 Gy) was performed, which resulted in radiologic disease stability for 3 months. Hereafter, a period of slow clinical decline followed and the patient passed away about 1 year after pancreatic cancer recurrence was detected

72.2.1 Biomarkers

CA 19-9 is currently the most widely assessed serum tumour marker for both diagnostic and surveillance purposes in pancreatic cancer care [22]. Before the introduction of CA 19-9 as an effective biomarker for pancreatic cancer, the carcinoembryonic antigen (CEA) was used. Nevertheless, CA 19-9 has been shown to be superior to CEA for surveillance after pancreatic cancer resection [23, 24]. Therefore, CEA has generally been replaced by CA 19-9 as the biomarker of choice in patients with pancreatic cancer.

CA 19-9 is a monoclonal antibody, raised against tumour-associated glycoproteins, which was initially detected from a colorectal cancer cell line [25]. In later research, CA 19-9 was found to be associated with pancreatic cancer [26]. In pancreatic cancer, elevation of CA 19-9 reflects increased production and secretion of this antigen from malignant cells [27]. However, CA 19-9 can also be elevated in other cancers, including hepatocellular, colorectal and ovarian cancers, and can be elevated in benign diseases as pancreatitis, choledocholithiasis and liver cirrhosis as well [26, 28–30]. Also, CA 19-9 was found to be increased in patients with obstructive jaundice [31].

For the primary detection of pancreatic cancer, CA 19-9 is not considered to be useful (see own chapter in this book) [32]. For predicting pancreatic cancer recurrence following resection, however, serum CA 19-9 was found to have a moderate value with a sensitivity of 68–89% and a specificity of 77–89% for detecting recurrence [22]. Several studies reported on a significant additional value of preoperative CA

19-9 levels >100 U/ml, CA 19-9 levels >50 U/ml adjusted to the serum bilirubin levels, elevated postoperative CA 19-9 levels and postoperative CA 19-9 velocity > 95 U/ml/4-weeks in predicting disease recurrence [23, 26, 33]. Herewith, serial CA 19-9 testing could be useful to inform patients on their prognosis and support shared decision making [34]. Furthermore, it was found that CA 19-9 elevation precedes evidence of recurrence on imaging by 3–6 months [21, 34]. As a consequence, it was suggested that CA 19-9 dynamics during surveillance could be used for tumour marker-guided chemotherapy, resulting in survival benefits [21]. A major limitation of CA 19-9, however, is that it is related to the Lewis blood group antigens. About 90–95% of patients belong to Lewis blood groups (i.e. Le (α−β+) or Le (α+β−)) that express the CA 19-9 antigen [28, 35]. Consequently, 5–10% of all patients do not express CA 19-9. In these patients, routine CA 19-9 measurements have no added value.

Other biomarkers reported in the literature that are related to pancreatic cancer are s-pancreas antigen-1 (SPan-1) and duke pancreatic monoclonal antigen type 2 (DU-PAN 2) [31, 36–41]. In contrast to CA 19-9, these biomarkers can be detected in Lewis antigen α- and β-negative individuals and could therefore be of particular interest in patients who are unable to synthesize CA 19-9. Just a few studies evaluating these potentially useful biomarkers are published, solely focusing on preoperatively measured values for the diagnosis of pancreatic cancer or prognostic purposes. As a consequence, the value of these tumour markers with regard to postoperative surveillance after pancreatic cancer resection is yet unknown.

72.2.2 Liquid Biopsies

In recent years, liquid biopsies have shown promise as a biomarker for the monitoring of tumour dynamics in several cancers [42]. With regard to pancreatic cancer, a growing interest in liquid biopsies for the measurement of circulating tumour DNA and circulating tumour cells exists as well [43–47]. A prospective study on circulating tumour cells in patients with resected pancreatic cancer showed that a rise in circulating tumour cells during surveillance was predictive of recurrence within 2 months [46]. Similarly, tumour-specific circulating tumour DNA predicted clinical disease recurrence and was shown to precede the detection of disease recurrence by imaging with a lead time of almost 3 months [45, 48]. Although such tests might be useful for surveillance after pancreatic cancer resection, no clinically applicable tests are yet available [49]. Current research focuses on further development of these promising detection methods.

72.2.3 Imaging

Imaging modalities that can be used to detect pancreatic cancer recurrence are CT imaging, PET-CT imaging and MRI. Of these, contrast-enhanced CT imaging is the preferred imaging modality to be applied during follow-up in clinical practice

[50–52]. The diagnostic accuracy of contrast-enhanced CT imaging for the detection of local and/or distant pancreatic cancer recurrence was found to be moderate, with a sensitivity of 70% and a specificity of 80% [53]. PET-CT showed a higher diagnostic performance, with a sensitivity and specificity of respectively 88% and 89% to detect and localize pancreatic cancer recurrence. A combination of contrast-enhanced CT and PET-CT further improves the sensitivity and specificity to 95% and 81%, respectively [53]. The additional value of PET-CT relates in particular to the ability to differentiate between postoperative fibrosis and recurrent tumour tissue, thus being specifically valuable in case of uncertain CT findings. Moreover, PET-CT can be useful in case of suspected clinical signs or tumour marker elevation with negative CT results [54–57]. The value of MRI as imaging modality during postoperative follow-up remains unknown, as no studies are published on its diagnostic accuracy for recurrence detection.

In most studies reporting on the diagnostic performance of imaging modalities for the detection of disease recurrence, further diagnostic imaging was performed based on a significant patient-initiated complaint or serum CA 19-9 elevation [56–58]. The value of routine follow-up imaging in the context of a standardized surveillance program was only evaluated in a few small, retrospective cohort studies [54, 55, 59, 60]. Nevertheless, these studies showed that routinely performed CT and PET-CT scans had a similar diagnostic accuracy as compared with scans that were performed when recurrence was clinically suspected [53].

72.2.4 Tissue Diagnosis

A common difficulty in the diagnosis of disease recurrence after pancreatic cancer resection is to obtain histological evidence of a suspicious lesion. This applies in particular to localized tumour recurrence within the pancreatic remnant or its surrounding structures. For the primary diagnosis of pancreatic cancer, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has shown to be a useful and accurate diagnostic tool [61]. In the diagnostic workup of pancreatic cancer recurrence, however, the value of EUS-FNA is poorly assessed. Two small, retrospective studies have been performed evaluating the diagnostic performance of EUS-FNA for pancreatic cancer recurrence. These studies suggested that EUS-FNA is useful for the diagnosis of disease recurrence, with a sensitivity ranging from 81 to 93% and a specificity of 100% [62, 63]. Nevertheless, it can be technically difficult to perform EUS-FNA after pancreatic resection both safely and successfully. Difficulties to differentiate between viable tumour tissue and postoperative fibrosis can impair visualisation of the target lesion. Moreover, success rates of biopsies to collect sufficient aspiration material for a definite histological diagnosis of pancreatic cancer recurrence remain unknown. As soft tissue around a major artery was found to be associated with a false negative diagnosis, the results of EUS-FNA need to be interpreted with care for these patients in particular [62].

72.3 Controversies

Current guidelines on surveillance after pancreatic cancer resection are based on expert opinion and other low-level evidence. Moreover, the cost-effectiveness of recurrence-focused surveillance and early treatment of cancer recurrence is increasingly being questioned in other types of cancer, such as ovarian and colorectal cancer [64, 65]. Prospective studies in these cancers did not found a significant disease-specific survival benefit of active surveillance. Unfortunately, the risk of disease recurrence after pancreatic cancer resection is much higher as compared with other cancer types. As a consequence, potential benefits of recurrence-focused surveillance might have a higher impact in pancreatic cancer patients. On the other hand, pancreatic cancer recurrence is notoriously difficult to treat as it is typically characterized by multifocal and destructive spread, possibly limiting the clinical benefit of additional treatment.

Few studies have been performed evaluating the direct impact of postoperative imaging surveillance on survival and quality of life. Herewith, it was found that annual follow-up imaging was not associated with improved survival [66]. However, survival benefits have been suggested with CT imaging at a 3–4 or 6 monthly interval during the first 2 years after surgery [18–20, 51]. It was shown that systematic CT-based follow-up at these intervals resulted in the detection of pancreatic cancer recurrence in an early, asymptomatic stage [18, 19]. Subsequently, patients with a good performance state and tumour biology that are most likely to benefit from further treatment could be identified. This strategy could allow for more aggressive oncological treatment in an increased number of patients while the tumour burden is still low, thus improving survival rates [18–20]. Furthermore, it was thought that early detection of pancreatic cancer recurrence could facilitate patient selection for clinical trials evaluating new therapies [18, 19]. Nevertheless, a simulation study on the cost-effectiveness of postoperative surveillance using data from patients who had received standardized imaging surveillance every 3–4 months showed that a limited surveillance strategy consisting of 6-monthly clinical evaluation and CA 19-9 testing was most cost-effective [67].

Considering quality of life outcomes, a structured surveillance was found to contribute to the optimization of symptom- and cancer-directed treatment, improving quality of life [17]. Moreover, patients seem to desire routine surveillance after pancreatic cancer resection, which was supported by pancreatic cancer clinicians as well [68]. In contrast, recurrence-focused surveillance might have some substantial disadvantages with regard to the patients' quality of life. Regular postoperative diagnostic testing is known to introduce significant psychological stress and fear of cancer recurrence [69, 70]. Moreover, diagnostic testing as well as additional treatment for recurrence can introduce significant morbidity, which may result in an overall decrease in quality of life. Also, it was found that with serial CA 19-9 measurements patients mainly focus on the test results during follow-up appointments, hampering discussions on other oncological and gastro-intestinal problems [71]. These (ethical) concerns are particularly important to account for when considering

Table 72.1 Recommendations regarding surveillance after pancreatic cancer resection in current guidelines

Organization	Recommended surveillance strategy	Level of evidence
ESMO (2015) [32]	No recurrence-focused surveillance	No evidence (4D)
IAP/EPC (2016) [73]	No recommendation	Not applicable
JPS (2016) [72]	Serum tumour marker testing and CT imaging every 3–6 months for 2 years after resection and every 6–12 months subsequently, at least for 5 years	Low (C)
NCCN (2018) [50]	History and physical examination for symptom assessment every 3–6 months for 2 years, then every 6–12 months on clinical indication	Uniform expert opinion (2A)
	CA 19-9 and follow-up CT imaging (chest, abdomen, and pelvis) with contrast every 3–6 months for 2 years	Non-uniform expert opinion (2B)
ASCO (2017) [74]	History and physical examination every 3–6 months after completion of therapy. Additional serum CA 19-9 testing if elevated pre-operatively	Low (C)
	No recommendations regarding the use of imaging procedures, surveillance intervals and duration	

ESMO European Society for Medical Oncology, *IAP/EPC* International Association of Pancreatology/European Pancreatic Club, *JPS* Japan Pancreas Society, *NCCN* National Comprehensive Cancer Network, *ASCO* American Society of Clinical Oncology

intensified surveillance in a patient population with such a limited life expectancy as with pancreatic cancer. Besides, frequent diagnostic testing increases the economic burden for both individual patients and society, while the cost-effectiveness of standardized surveillance for the early detection and treatment of pancreatic cancer recurrence is yet unclear.

As a result of these controversies, widely varying surveillance strategies are applied throughout the world (Table 72.1). Guidelines by the National Comprehensive Cancer Network (NCCN) and Japanese Pancreas Society (JPS) do recommend standardized surveillance with serum CA 19-9 testing and imaging every 3–6 months during the first 2 years after pancreatic resection [50, 72]. Contrastingly, guidelines by the European Society for Medical Oncology (ESMO), the International Association of Pancreatology/European Pancreatic Club (IAP/EPC) and American Society of Clinical Oncology (ASCO) provide minimal guidance on method, frequency and duration of postoperative surveillance [32, 73, 74].

72.4 Future Research

Results of previous studies on potential survival and quality of life benefits of standardized surveillance after pancreatic cancer resection are conflicting. Furthermore, the current evidence mainly consists of small, retrospective studies.

This has led to significantly different surveillance strategies being applied in clinical practice, potentially depriving certain patients from meaningful surveillance, whilst others might be wrongfully harmed. Most available studies were performed before the introduction of recent, more potent treatment options. More recent studies, however, suggest that surveillance with tumour marker testing and imaging at regular intervals contributes to the early detection of pancreatic cancer recurrence, before the onset of symptoms. This can increase the number of patients with a good performance state eligible for further therapy such as chemotherapy or radiotherapy. As a result, pancreatic cancer centres worldwide increasingly implement a standardized surveillance strategy with serum CA 19-9 testing and CT imaging, every 3–6 months during the first 2 years after resection. At the end of 2018, the PRODIGE Group published impressive results of modified FOLFIRINOX chemotherapy as adjuvant chemotherapy for patients with resected pancreatic cancer [15]. However, the control group, in which patients received adjuvant gemcitabine, also showed considerably high survival rates as compared with other phase three trials performed on this subject (35 months vs. 20–27 months). The authors suggested that this could be due to the use of FOLFIRINOX as recurrence treatment in the majority of patients (76%) that were diagnosed with pancreatic cancer recurrence in the gemcitabine group. When discussing on the value of standardized postoperative surveillance, potentially improved perspectives for pancreatic cancer patients following treatment with FOLFIRINOX chemotherapy therefore need to be considered. To provide recommendations on postoperative surveillance, however, high-quality evidence from prospective studies comparing different surveillance strategies on the true value of recurrence-focused surveillance are needed.

72.5 Conclusion

In summary, surveillance after surgery for pancreatic cancer remains a subject of discussion, with an ongoing effort to improve both the detection and treatment of pancreatic cancer recurrence. Although the true value of standardized postoperative surveillance has yet to be established, a surveillance strategy existing of 3-6 monthly serum CA 19-9 testing and CT imaging during the first 2 years after surgery is increasingly implemented.

References

1. Groot VP, Rezaee N, Wu W, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg. 2018;267:936–45.
2. Groot VP, Gemenetzis G, Blair AB, et al. Implications of the pattern of disease recurrence on survival following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2018;25(8):2475–83.

3. Jones RP, Psarelli EE, Jackson R, et al. European Study Group for Pancreatic Cancer. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019;154(11):1038–48. https://doi.org/10.1001/jamasurg.2019.3337.
4. Sperti C, Moletta L, Merigliano S. Multimodality treatment of recurrent pancreatic cancer: mith or reality? World J Gastrointest Oncol. 2015;7(12):375e82.
5. Daamen LA, Groot VP, Intven MPW, et al. Postoperative surveillance of pancreatic cancer patients. Eur J Surg Oncol. 2019;45(10):1770–7.
6. Groot VP, Gemenetzis G, Blair AB, et al. Defining and predicting early recurrence in 957 patients with resected pancreatic ductal adenocarcinoma. Ann Surg. 2019;269:1154–62.
7. Wu W, He J, Cameron JL. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol. 2014;21(9):2873–81.
8. Mackay TM, Smits FJ, Roos D, et al. The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis. HPB (Oxford). 2020;22(2):233–40. pii: S1365-182X(19)30610-0.
9. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389:1011–24.
10. Groot VP, Blair AB, Gemenetzis G, et al. Recurrence after neoadjuvant therapy and resection of borderline resectable and locally advanced pancreatic cancer. Eur J Surg Oncol. 2019;45(9):1674–83.
11. Chawla A, Molina G, Pak LM, et al. Neoadjuvant therapy is associated with improved survival in borderline-resectable pancreatic cancer. Ann Surg Oncol. 2020;27(4):1191–20.
12. Versteijne E, Vogel JA, Besselink MG, et al. Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946–58.
13. Groot VP, Daamen LA, Hagendoorn J, Borel Rinkes IHM, van Santvoort HC, Molenaar IQ. Use of imaging during symptomatic follow-up after resection of pancreatic ductal adenocarcinoma. J Surg Res. 2018;221:152–60.
14. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. HPB (Oxford). 2017;19(2):83–92.
15. Conroy T, Hammel P, Hebbar M, et al. Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
16. Ryan JF, Groot VP, Rosati LM, et al. Stereotactic body radiation therapy for isolated local recurrence after surgical resection of pancreatic ductal adenocarcinoma appears to be safe and effective. Ann Surg Oncol. 2018;25(1):280–9.
17. Tjaden C, Michalski CW, Strobel O, et al. Clinical impact of structured follow-up after pancreatic surgery. Pancreas. 2016;45(6):895–9.
18. Nordby T, Hugenschmidt H, Fagerland MW, Ikdahl T, Buanes T, Labori KJ. Follow-up after curative surgery for pancreatic ductal adenocarcinoma: asymptomatic recurrence is associated with improved survival. Eur J Surg Oncol. 2013;39:559–66.
19. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. HPB (Oxford). 2012;14:365–72.
20. Elmi A, Murphy J, Hedgire S, et al. Post-Whipple imaging in patients with pancreatic ductal adenocarcinoma: association with overall survival: a multivariate analysis. Abdom Radiol. 2017;42:2101–7.
21. Li J, Li Z, Kan H, et al. CA19-9 elevation as an indication to start salvage treatment in surveillance after pancreatic cancer resection. Pancreatology. 2019;19:30024e9. pii: S1424-3903.

22. Daamen LA, Groot VP, Heerkens HD, Intven MPW, van Santvoort HC, Molenaar IQ. Systematic review on the role of serum tumor markers in the detection of recurrent pancreatic cancer. HPB (Oxford). 2018;20:297e304.
23. Osayi SN, Bloomston M, Schmidt CM, Ellison EC, Muscarella P. Biomarkers as predictors of recurrence following curative resection for pancreatic ductal adenocarcinoma: a review. Biomed Res Int. 2014;2014:468959.
24. Winter JM, Yeo CJ, Brody JR. Diagnostic, prognostic, and predictive biomarkers in pancreatic cancer. J Surg Oncol. 2013;107:15–22.
25. Koprowski H, Herlyn M, Steplewski Z, Sears HF. Specific antigen in serum of patients with colon carcinoma. Science. 1981;212:53–5.
26. Kang CM, Kim JY, Choi GH, et al. The use of adjusted preoperative CA 19-9 to predict the recurrence of resectable pancreatic cancer. J Surg Res. 2007;140:31–5.
27. Fry LC, Monkemuller K, Malfertheiner P. Molecular markers of pancreatic cancer: development and clinical relevance. Langenbecks Arch Surg. 2008;393:883–90.
28. Distler M, Pilarsky E, Kersting S, Grutzmann R. Preoperative CEA and CA 19-9 are prognostic markers for survival after curative resection for ductal adenocarcinoma of the pancreas – a retrospective tumor marker prognostic study. Int J Surg. 2013;11:1067–72.
29. Lamerz R. Role of tumour markers, cytogenetics. Ann Oncol. 1999;10(Suppl 4):145–9.
30. Galli C, Basso D, Plebani M. CA 19-9: handle with care. Clin Chem Lab Med. 2013;51:1369–83.
31. Hosokawa Y, Nagakawa Y, Sahara Y, Takishita C, Katsumata K, Tsuchida A. Serum SPan-1 is a significant risk factor for early recurrence of pancreatic cancer after curative resection. Dig Surg. 2017;34:125–32.
32. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
33. Nakagawa K, Akahori T, Nishiwada S, et al. Prognostic factors for actual long-term survival in the era of multidisciplinary treatment for pancreatic ductal adenocarcinoma. Langenbecks Arch Surg. 2018;403(6):693–700.
34. Rieser CJ, Zenati M, Hamad A, et al. CA19-9 on postoperative surveillance in pancreatic ductal adenocarcinoma: predicting recurrence and changing prognosis over time. Ann Surg Oncol. 2018;25(12):3483–91.
35. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res. 1987;47:5501–3.
36. Nishio K, Kimura K, Amano R, et al. Preoperative predictors for early recurrence of resectable pancreatic cancer. World J Surg Oncol. 2017;15(1):16-016-1078-z.
37. Kiriyama S, Hayakawa T, Kondo T, et al. Usefulness of a new tumor marker, Span-1, for the diagnosis of pancreatic cancer. Cancer. 1990;65(7):1557–61.
38. Chung YS, Ho JJ, Kim YS, et al. The detection of human pancreatic cancer-associated antigen in the serum of cancer patients. Cancer. 1987;60(7):1636–43.
39. Kondo N, Murakami Y, Uemura K, et al. Comparison of the prognostic impact of pre- and post-operative CA19-9, SPan-1, and DUPAN-II levels in patients with pancreatic carcinoma. Pancreatology. 2017;17(1):95–102.
40. Satake K, Takeuchi T. Comparison of CA19-9 with other tumor markers in the diagnosis of cancer of the pancreas. Pancreas. 1994;9(6):720–4.
41. Kawa S, Oguchi H, Kobayashi T, et al. Elevated serum levels of Dupan-2 in pancreatic cancer patients negative for Lewis blood group phenotype. Br J Cancer. 1991;64(5):899–902.
42. Husain H, Velculescu VE. Cancer DNA in the circulation: the liquid biopsy. JAMA. 2017;318(13):1272–4.
43. Stroese AJ, Ullerich H, Koehler G, Raetzel V, Senninger N, Dhayat SA. Circulating microRNA-99 family as liquid biopsy marker in pancreatic adenocarcinoma. J Cancer Res Clin Oncol. 2018;144(12):2377–90.
44. Court CM, Ankeny JS, Sho S, et al. Circulating tumor cells predict occult metastatic disease and prognosis in pancreatic cancer. Ann Surg Oncol. 2018;25(4):1000–8.

45. Groot VP, Mosier S, Javed AA, et al. Circulating tumor DNA as a clinical test in resected pancreatic cancer. Clin Cancer Res. 2019;25(16):4973–84.
46. Gemenetzis G, Groot VP, Yu J, et al. Circulating tumor cells dynamics in pancreatic adenocarcinoma correlate with disease status: results of the prospective CLUSTER study. Ann Surg. 2018;268(3):408e20.
47. Creemers A, Krausz S, Strijker M, et al. Clinical value of ctDNA in upper-GI cancers: a systematic review and meta-analysis. Biochim Biophys Acta Rev Cancer. 2017;1868(2):394e403.
48. Watanabe F, Suzuki K, Tamaki S, et al. Longitudinal monitoring of KRAS-mutated circulating tumor DNA enables the prediction of prognosis and therapeutic responses in patients with pancreatic cancer. PLoS One. 2019;14(12):e0227366.
49. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018;36(16):1631e41.
50. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic Adenocarcinoma, Version 1.2019. J Natl Compr Cancer Netw. 2019;17(3):202–10.
51. Balaj C, Ayav A, Oliver A, et al. CT imaging of early local recurrence of pancreatic adenocarcinoma following pancreaticoduodenectomy. Abdom Radiol. 2016;41:273–82.
52. Bipat S, Phoa SS, van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. J Comput Assist Tomogr. 2005;29:438–45.
53. Daamen LA, Groot VP, Goense L, et al. The diagnostic performance of CT versus FDG PET-CT for the detection of recurrent pancreatic cancer: a systematic review and meta-analysis. Eur J Radiol. 2018;106:128–36.
54. Kitajima K, Murakami K, Yamasaki E, et al. Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent pancreatic cancer: comparison with integrated FDG-PET/non-contrast-enhanced CT and enhanced CT. Mol Imaging Biol. 2009;12(4):452–9.
55. Jung W, Jang JY, Kang MJ, et al. The clinical usefulness of 18 ffluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) in followup of curatively resected pancreatic cancer patients. HPB. 2015;17:165–6.
56. Rayamajhi S, Balachandran A, Katz M, Reddy A, Rohren E, Bhosale P. Utility of (18) F-FDG PET/CT and CECT in conjunction with serum CA 19-9 for detecting recurrent pancreatic adenocarcinoma. Abdom Radiol (NY). 2018;43(2):505–13.
57. Jadvar H, Fischman AJ. Evaluation of pancreatic carcinoma with FDG PET. Abdom Imaging. 2001;26:254–9.
58. Peti S, Fardanesh R, Golan S, et al. The combination of FDG PET/CT and contrast enhanced CT in the evaluation of recurrent pancreatic carcinoma and cholangiocarcinoma. Curr Med Imaging Rev. 2014;10:53–61.
59. Mortelé KJ, Lemmerling M, De Hemptinne B, De Vos M, De Bock G, Kunnen M. Postoperative findings following the Whipple procedure: determination of prevalence and morphologic abdominal CT features. Eur Radiol. 2000;10:123–8.
60. Sperti C, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. 18-FDG PET performs much better than CT in detecting tumor relapse after potentially curative pancreatic cancer resection and it may influence long-term outcomes. Pancreatology. 2009;9:444.
61. Chang KJ, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. Gastrointest Endosc. 1997;45(5):387–93.
62. Matsumoto K, Kato H, Horiguchi S, et al. Utility of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of local recurrence of pancreaticobiliary cancer after surgical resection. Gut Liver. 2019; https://doi.org/10.5009/gnl19200.
63. DeWitt J, Sherman S, Al-Haddad M, McHenry L, Cote GA, Leblanc JK. EUS-guided FNA of local recurrence of pancreatic cancer after surgical resection. Gastrointest Endosc. 2010;72(5):1076–80.

64. Bastiaenen VP, Hovdenak Jakobsen I, Labianca R, et al. Research Committee and the Guidelines Committee of the European Society of Coloproctology (ESCP). Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology. Color Dis. 2019;21(4):392–416.
65. Rustin GJ, van der Burg ME, Griffin CL, et al. MRC OV05; EORTC 55955 investigators. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet. 2010;376(9747):1155–63.
66. Witkowski ER, Smith JK, Ragulin-Coyne E, Ng SC, Shah SA, Tseng JF. Is it worth looking? Abdominal imaging after pancreatic cancer resection: a national study. J Gastrointest Surg. 2012;16:121–8.
67. Tzeng CW, Abbott DE, Cantor SB, et al. Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis. Ann Surg Oncol. 2013;20:2197–203.
68. Deobald RG, Cheng ES, Ko YJ, Wright FC, Karanicolas PJ. A qualitative study of patient and clinician attitudes regarding surveillance after a resection of pancreatic and peri-ampullary cancer. HPB (Oxford). 2015;17:409–15.
69. Deimling GT, Bowman KF, Sterns S, Wagner LJ, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. Psychooncology. 2006;15:306–20.
70. Petzel MQ, Parker NH, Valentine AD, et al. Fear of cancer recurrence after curative pancreatectomy: a cross-sectional study in survivors of pancreatic and periampullary tumors. Ann Surg Oncol. 2012;19:4078–84.
71. Elberg Dengsø K, Tjørnhøj-Thomsen T, Oksbjerg Dalton S, et al. It's all about the CA-19-9. A longitudinal qualitative study of patients' experiences and perspectives on follow-up after curative surgery for cancer in the pancreas, duodenum or bile-duct. Acta Oncol. 2019;58(5):642–9.
72. Yamaguchi K, Okusaka T, Shimizu K, et al. EBM-based clinical guidelines for pancreatic cancer (2013) issued by the Japan pancreas society: a synopsis. Jpn J Clin Oncol. 2014;44:883e8.
73. Takaori K, Bassi C, Biankin A, et al. International Association of Pancreatology (IAP)/ European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. Pancreatology. 2016;16:14–27.
74. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(20):2324–8.

Chapter 73
Survival After Resection for Pancreatic Cancer

Cristina R. Ferrone and Yurie Sekigami

Take Home Messages

- Factors associated with 5-year survival in multivariate analyses consistently include lymph node status and negative resection margins.
- Pancreatic cancer is a systemic disease and systemic adjuvant or neoadjuvant therapies are therefore invaluable in improving survival.
- Neoadjuvant or adjuvant FOLFIRINOX improves the overall survival of patients with pancreatic adenocarcinoma.
- Patient-reported outcomes after pancreatic resection help inform decision-making and aid in managing patients' perioperative expectations.

Future Perspectives

- An improved understanding of the biology of pancreatic cancer to allow for treatment paradigms
- Early detection of pancreatic cancer through new diagnostic modalities such as screening of microRNA, liquid biopsies for proteomic analysis and other biomarkers
- Improved understanding of the genetic or biologic risk factors for pancreatic cancer
- Elucidation of factors that may predict early postoperative recurrence which may allow patients to forgo highly morbid surgery

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73.1 Introduction

The incidence of pancreatic cancer continues to rise with an estimated 62,000 cases in the United States in 2020 [1]. Although resection offers the only chance for cure in pancreatic ductal adenocarcinoma (PDAC), 5-year survival after surgical resection, while improving, remains low at 13–27% [2].

This chapter gives an overview of survival (Box 73.1) measures for patients having surgery for PDAC and factors associated with survival times in the current treatment landscape.

Box 73.1 Types of Survival

- **Disease-free survival**: The percentage of patients in complete remission after completing curative treatment
- **Recurrence-free survival**: The percentage of patients who do not experience recurrence after completing curative treatment
- **Cancer-specific survival**: The percentage of patients who have not died from a specific cancer in a defined period of time after diagnosis or start of treatment. Patients who died from causes other than the specific type of cancer are not counted in this measurement
- **Overall survival**: The percentage of patients who are alive at a certain time after diagnosis
- **Relative survival**: The overall survival of patients who have a disease divided by the overall survival of patients who do not have the disease
- **Conditional survival**: The percentage of patients surviving an additional number of years given that they have already survived a certain amount of time after surgery or diagnosis

73.2 Independent Predictors of 5-Year Survival After Surgery for PDAC

73.2.1 Surgical Margins

Similar to many other solid cancers, negative surgical margins (R0 resection) correlate with long-term survival [3–7]. Notably, prior retrospective studies and phase III clinical trials demonstrate that patients who have a macroscopically positive margin after resection have a survival similar to that of patients who do not undergo an operation [8, 9], and planned tumor debulking is therefore not recommended in pancreatic cancer. However, even with surgically negative margins, 5-year survival rates after pancreaticoduodenectomy are 10–25% with a median survival between 10–20 months [10–15]. In the ESPAC-3 trial, a negative resection margin was associated with improved survival on univariate survival analysis among patients who received either fluorouracil plus folinic acid or gemcitabine as adjuvant therapy. The

increased risk of death in patients with positive margins compared with patients with negative margins was 35% [16]. However, in a series of 141 patients who received neoadjuvant FOLFIRINOX followed by radiation therapy at Massachusetts General Hospital, surgical margins were not found to be predictive of overall survival in those patients who were successfully resected [17].

73.2.2 Nodal Status

In patients with completely resected PDAC, one of the most significant prognostic factors is nodal status. Five-year survival for those with node-positive disease is approximately 10%, whereas those with node-negative disease have a 30% chance of surviving 5 years [18]. A review of a prospectively maintained database of 618 patient who underwent pancreatic resection for PDAC at Memorial Sloan-Kettering Cancer Center revealed that early American Joint Committee on Cancer (AJCC) stage ($p < 0.001$) and negative margins ($p = 0.001$) were associated with 5-year survival [6]. At Massachusetts General Hospital, Ferrone et al. demonstrated that negative margins and negative nodal status were predictors of 5- and 10-year survival [19]. Katz and colleagues found negative lymph node status to be significantly associated with 5-year survival (odds ratio 1.92, $p = .02$) on multivariate analysis in patients with resected PDAC [20]. In a retrospective study of 519 patients who underwent pancreatic resection for adenocarcinoma, Konstantinidis and colleagues found that patients with one positive lymph node fared better than those with greater than one positive lymph node [21]. They also demonstrated that node involvement by metastasis or direct invasion were equally significant predictors of reduced survival. In a recent retrospective study of 546 patients with resected PDAC, median overall survival for pN0 patients was found to be significantly longer than pN1 patients. In addition, time to recurrence was significantly longer in pN0 compared to pN1 patients [22].

Number of nodes sampled has contributed to improved survival stratification. Multiple studies have demonstrated that patients with less than 10–12 lymph nodes sampled with pN0 disease have worse survival outcomes compared with those who had greater than 10–12 nodes sampled [23–25]. Given the improved patient stratification associated with an increased number of nodes sampled, extended lymphadenectomy (removal of nodes up to the hepatic hilum and para-aortic region from the diaphragmatic hiatus to the level of the inferior mesenteric arteries) has been proposed to improve outcomes. However, multiple studies including a recent meta-analysis demonstrated that extended lymphadenectomy does not improve overall survival compared to standard lymphadenectomy, but rather leads to increased morbidity [26–28].

Although some institutions have explored extended pancreatic resection to include vascular resection and retroperitoneal lymphadenectomy, a prospective trial performed by Michalski and colleagues demonstrated that extended operations in patients who have not received neoadjuvant therapy leads to increased morbidity and mortality without survival benefit [27, 29].

73.2.3 Tumor Pathology

Tumor size and grade have both been implicated as important prognostic factors for patients with resectable PDAC [30]. Upon multivariate analysis, Han and colleagues found that tumor size (HR 5 1.38, p 5 0.03) and tumor differentiation (HR 5 0.76, p 5 0.02) affected long-term survival in PDAC patients after resection [4]. With regards to size, a study from the Mayo clinic found survival is significantly better in small pancreatic cancers (<2 cm) with regional nodal metastasis (stage III) compared with similar stage large pancreatic cancers (5-year survival 44 vs 7%, medial survival 58 vs 18 months, $p < 0.001$). However, there was no survival difference regardless of tumor size in patients with small pancreatic cancers and localized disease (stage I and II) compared with large pancreatic cancers with similar stages [31]. Size greater than 2.5 cm on pathology was an independent predictor of decreased overall survival in patients who received neoadjuvant FOLFIRINOX followed by chemoradiation and then underwent resection in the MGH series of 141 patients [17].

73.2.4 Patient Factors

Patients undergoing resection for PDAC today are generally older and have more comorbidities than those who underwent resection 30 years ago [32]. A study performed by Dias-Santos et al. demonstrated that an age-adjusted Charlson Age Comorbidity Index of ≥6 increased the odds of death threefold within the first year after resection [33]. Recently, Hank et al. identified that diabetes was associated with a worse median overall survival, larger tumors, and higher rates of lymph node involvement and perineural invasion [34].

Even in the era of neoadjuvant therapy, comorbidities seem to be predictive of outcome. Michelakos et al. found that after neoadjuvant FOLFIRINOX, Charlson comorbidity index >1 predicted decreased overall survival [17].

73.2.5 CA 19-9 Levels

CA 19-9 has been shown to correlate with tumor burden, with higher preoperative levels (>180 U/mL) correlating with adverse pathologic features and poorer survival [35]. Ferrone et al. demonstrated that a postoperative decrease in addition to a postoperative CA 19-9 value of less than 200 U/mL were strong independent predictors of survival [36]. Patients with a preoperative CA 19-9 < 1000 U/mL had a significantly longer median survival (2.3 years versus 1 year). Patients with resected PDAC and postoperative CA 19-9 ≥ 180 U/mL had significantly worse survival and were 3.5 times more likely to die from recurrence than those patients with CA 19-9 < 180 U/mL in a study conducted by Berger and colleagues [37].

Trend in perioperative CA 19-9 also confers important prognostic value. Normalization of levels postoperatively was associated with a superior prognosis in multiple studies [38, 39], while the failure of levels to normalize postoperatively may have a negative impact on survival [36, 40]. A study from University of Pittsburgh identified five different patterns of CA 19-9 beyond the post-resection period. Persistent normalization was an independent predictor of survival (HR, 0.44; $p = 0.001$) and the always-elevated pattern was negatively associated with survival (HR, 3.31; $p = <0.001$). Conditional overall survival analysis revealed that elevated CA 19-9 was associated with worse survival at each time point and that the impact of CA 19-9 status increased over time [41].

CA 19-9 levels in response to neoadjuvant therapy also has implications for survival. A CA 19-9 response of >50% was associated with improved overall survival and was an independent predictor of survival [42].

73.2.6 Circulating Tumor DNA

There has been increasing interest in the development of non-invasive biomarkers for prognostication in pancreatic cancer. Circulating tumor DNA (ctDNA) has emerged as a promising prognostic biomarker in various cancers, and multiple studies have investigated its role in PDAC [43, 44]. A recent meta-analysis revealed detectable pre- or post- operative ctDNA in resectable PDAC has a significant negative effect on both overall and disease-free survival [45].

73.3 Conditional Survival

More contemporary studies have investigated the conditional survival of pancreatic cancer patients, which embraces the notion that survival is a dynamic and not a static concept. A study performed at Johns Hopkins of 1822 patients revealed that the conditional 2-year survival of patients who already survived three years was 66%, whereas the actuarial 5-year survival of all patients after resection was 18%. When conditional survival was stratified by lymph node ratio, there was a more notable increase in 2-year conditional survival over time when comparing patients with N0 disease or a low lymph node ratio (<0.132) versus patients with a high lymph node ratio (>0.307). They also discovered that patients with R1/R2 disease saw the greatest increases in 2-year conditional survival as more time elapsed [46]. A similar bi-institutional study of patients undergoing pancreatectomy for PDAC showed similar trends between conditional and overall survival, and also found that when stratified by the levels of prognostic covariates, the 60-months conditional survival estimates for disease-free patients tended to level off progressively, indicating the factors independently associated with survival at time of pancreatectomy lost power over time [47].

73.4 Neoadjuvant and Adjuvant Therapy

Pancreatic cancer is a systemic disease which requires systemic treatment in addition to localized surgical control, regardless of stage of disease. This chapter will focus on the major findings of the key trials demonstrating the survival benefit of neoadjuvant and adjuvant therapies in the setting of patients who undergo resection with curative intent (Box 73.2).

Box 73.2 Key Trials in Adjuvant Therapy

- GITSG trial: adjuvant 5-FU-based chemotherapy + radiotherapy followed by 2 years of 5-FU resulted in 21-month survival compared to 10 months with observation alone ($p = .03$) [48].
- RTOG-9704 trial: no significant difference in survival between gemcitabine with fluorouracil before and after fluorouracil-based chemoradiation [49].
- CONKO-001 trial: improvement in survival with 6 months of adjuvant gemcitabine chemotherapy versus observation after surgical resection (median 22.8 months vs 20.2 months; $p = .01$) [50].
- ESPAC-3: significantly better overall survival for patients who receive adjuvant 5FU/folinic acid (HR .70, $p = .003$) compared with surgery alone [51].
- ESPAC-4: significantly improved median overall survival in patients who received adjuvant gemcitabine plus capecitabine versus gemcitabine alone (28 vs 25.5 months) [52].
- PRODIGE 24/CCTG PA.6 trial: adjuvant therapy with a modified FOLFIRINOX regimen resulted in significantly longer disease-free and overall survival compared to gemcitabine among patients with pancreatic cancer who received an R0 or R1 resection. However, this gain in survival came at the expense of a higher incidence of adverse events [53].

73.4.1 Neoadjuvant Therapy

Neoadjuvant therapy is attractive for pancreatic cancer given the significant morbidity and mortality associated with surgical treatment. Because of the significant morbidity of pancreatic resections, up to one-third of patients will not receive adjuvant therapy. Neoadjuvant treatment offers multiple benefits including the ability to better understand the biology of disease, decrease the incidence of microscopically positive margins and leaks from the pancreatic-enteric anastomoses, and allows for a higher proportion of patients to receive systemic therapy [2].

A combination of chemoradiotherapy and isolated chemotherapy has been the longstanding neoadjuvant regimen for patients with PDAC. Photon therapy (50.4 Gy) is frequently utilized to downsize borderline or locally advanced tumors

to become resectable [2]. Concomitant chemotherapy typically consists of 5-fluorouracil, capecitabine, or gemcitabine at radiosensitizing doses. Isolated chemotherapy consists of gemcitabine alone or in combination or FOLFIRINOX. While a majority of the literature on neoadjuvant therapy are observational studies in patients with locally advanced disease [54–58], phase III trials comparing neoadjuvant chemotherapy and chemoradiation to upfront resection for resectable PDAC are underway.

Due to encouraging results from phase III trials showing significant improvement in overall survival in patients with metastatic disease utilizing FOLFIRINOX or gemcitabine/abraxane [59–61], patients with borderline resectable and locally advanced disease have also been treated with these regimens in the neoadjuvant setting. At Massachusetts General Hospital, two recent phase 2 trials were conducted yielding promising results. The first was a single-arm trial which included 48 patients with newly diagnosed borderline resectable PDAC who received neoadjuvant FOLFIRINOX followed by individualized chemoradiotherapy. Among the 32 patients who underwent resection, the R0 resection rate was 97% and their median progression-free survival was 48.6 months [62]. The second phase 2 trial was a single-arm trial which included 49 patients with newly diagnosed locally advanced PDAC who received neoadjuvant FOLFIRINOX and losartan followed by chemoradiotherapy. Among the 42 patients who underwent resection, the R0 resection rate was 69%, their median progression-free survival was 17.5 months, and their median overall survival was 33 months [63].

73.5 Five-Year Survivors After Resection

Multiple large series have been published in the past 20 years demonstrating improvement in 5-year survival. A retrospective study of 116 patients who underwent surgical resection of PDAC found a median survival of 16 months and a 5-year survival rate of 19%. Adjuvant therapy was the only feature found to be strongly associated with survival in multivariable analysis [64]. In a retrospective review of 123 patients who underwent surgical resection of PDAC for curative intent, Cleary et al. found a median survival of 14 months and 14% and 4% 5- and 10-year survival rates, respectively. AJCC stage and grade were independently associated with survival in multivariate analysis [65]. At Johns Hopkins, Winter et al. examined 1175 patients who underwent pancreaticoduodenectomy for PDAC and found a median survival of 18 months and 18% and 11% 5- and 10-year survival rates, respectively. In this large cohort, pathological factors having a significant impact on survival included tumor diameter, resection margin status, lymph node status, and histologic grade [3]. Han et al. analyzed 242 patients who underwent surgical resection with curative intent and found a median survival and 5-year survival rate of 14.8 months and 12.1%. AJCC stage and margin status were significant prognostic factors [4]. At Memorial Sloan-Kettering, 618 patients underwent resection for PDAC between 1983–2001, and among them, median survival was 20 months and 5- and 10-year

survival were 12% and 5%. Negative margins and AJCC stage were associated with 5-year survival [6]. At Massachusetts General Hospital, Ferrone et al. conducted a retrospective study of 499 patients who underwent resection for PDAC and found their median survival to be 19 months with 19% and 10% 5- and 10-year survival. In this cohort, margin status (as R0) and pN-stage (as pN0) predicted improved 5- and 10-year survival [19].

73.6 Surveillance

The National Comprehensive Cancer Network recommends surveillance history and physical examination along with CA 19-9 level and abdominal CT scan with contrast every 3–6 months for the first 2 years after an operation, then every 6–12 months thereafter. No specific guidelines exist to address recurrence in long-term survivors, but treatment considerations differ depending on the nature and location of recurrence. A recent retrospective study found median survival of patients with isolated recurrence was longer in patients who underwent surgical resection than among those treated non-surgically (23.5 versus 12.0 months; $p = 0.014$) and multivariable analysis showed that chemotherapy and resection for recurrence were associated with better prognosis [66].

73.7 Patient-Reported Postoperative Outcomes

With the expansion of pancreatoduodenectomies to include benign and premalignant lesions, there is growing interest in patient-reported outcomes of post-pancreatectomy patients. While most of these studies are limited by short follow-up durations and suboptimal response rates [67–70] (Table 73.1), one study by Fong and colleagues successfully surveyed 305 patients who were alive five years after undergoing pancreatoduodenectomy using the EORTC QLQ-C30 questionnaire, a validated quality-of-life instrument. Patients who underwent pancreatoduodenectomy demonstrated better global quality of life and physical- and role-functioning scores at 5 years when compared with age and sex-matched controls [71].

In Ontario, Canada, routine prospective collection of patient-reported Edmonton Symptom Assessment System (ESAS) scores during all outpatient cancer clinic visits was initiated in 2007. Tung and colleagues utilized this data to examine symptom trajectories over time and determine factors associated with moderate to severe symptom burden in the first year following pancreatoduodenectomy for PDAC. Six-hundred and fifteen patients were included. As one would expect, the proportion of patients with moderate to severe symptoms was highest immediately after the operation and decreased over time. Female sex, higher comorbidity, and lower income were associated with a higher risk of reporting moderate to severe symptoms, and receipt of adjuvant chemotherapy was not associated with the risk of moderate to severe symptoms [72].

Table 73.1 Studies examining postoperative patient-reported outcome measures after resection of pancreatic adenocarcinoma

Study	Patients (N)	Patient population	Control	Follow-up time	Response rate	PROM tool	Major findings
Tung et al. [72]	615	Patients undergoing PD for PDAC (those who received neoadjuvant therapy were excluded)	None	Up to 1 year	87%	Edmonton Symptom Assessment System (ESAS)	• Tiredness, impaired well-being, and lack of appetite were most commonly reported as moderate to severe • The proportion of patients with moderate to severe symptoms was highest immediately after surgery and decreased over time, stabilizing around 3 months • Female sex, higher comorbidity, and lower income were associated with a higher risk of reporting moderate to severe symptoms • Receipt of adjuvant chemotherapy was not associated with the risk of moderate to severe symptoms
Fong et al. [71]	245	Patients who underwent PD for neoplasms	Age- and sex-matched EORTC controls	Median 9.1 years	80.3%	EORTC QLQ-C30 questionnaire	• New-onset diabetes developed in 10.6% patients • 50.4% of patients reported taking pancreatic enzymes; 54.6% reported needing antacids • Compared with the age- and sex-adjusted controls, PD survivors demonstrated higher global QOL, physical and role-functioning scores

(continued)

Table 73.1 (continued)

Study	Patients (N)	Patient population	Control	Follow-up time	Response rate	PROM tool	Major findings
							• Using linear regression and adjusting for socioeconomic variables, there were no differences in QOL or functional scores in the benign versus malignant subgroups • Older age at operation was associated with worse physical-functioning • Taking pancrelipase or antacids were both associated with lower social functioning scores
Schniewind et al. [67]	91	Patients who underwent classical partial pancreaticoduodenectomy (PPD) and pylorus-preserving pancreaticoduodenectomy (PPPD) in for adenocarcinoma of the pancreatic head	None	Up to 2 years	53–73%	EORTC QLQ-C30 questionnaire and a pancreatic cancer-specific module	• QOL was impaired for 3–6 months after surgery and then recovered to preoperative levels • Patients who had extended lymphadenectomy reported clinically significant higher levels of diarrhea and pain • PPPD showed a disadvantage in terms of pain

Study	Patients (N)	Patient population	Control	Follow-up time	Response rate	PROM tool	Major findings
Cloyd et al. [68]	217	Recurrence-free survivors of PDAC, periampullary carcinomas, and pancreatic neuroendocrine tumors who underwent pancreatectomy (excluded patients who were within 6 months of surgery or developed recurrence)	None	Median 53.3 months	66%	Functional Assessment of Cancer Therapy—Hepatobiliary Questionnaire	• Overall QOL scores were favorable and influenced by race, histology, and type of surgery • Most common significant symptoms reported were fatigue, back pain, and difficulty with digestion • In general, PD survivors reported better QOL, lower levels of anxiety/depression, greater levels of diarrhea, and improved appetite, constipation, fatigue, anxiety, and depression than distal pancreatectomy survivors • Distal pancreatectomy was negatively associated with QOL

(continued)

Table 73.1 (continued)

Study	Patients (N)	Patient population	Control	Follow-up time	Response rate	PROM tool	Major findings
Huang et al. [69]	192	Patients who underwent PD for various malignant and benign diseases of the pancreas and periampullary region	Age- and sex-matched laparoscopic cholecystectomy patients and healthy controls	Median 41 months	59%	QOL survey instrument as defined by Ferrell et al. [73]	• Overall QOL scores for the PD patients were comparable to those of laparoscopic cholecystectomy patients and healthy controls • Patients who underwent resection for chronic pancreatitis and PDAC had significantly lower QOL scores in the physical and psychological domains compared with the laparoscopic cholecystectomy patients and the healthy controls • Common problems after PD were weight loss, abdominal pain, fatigue, foul stools, and diabetes
Pezzilli et al. [70]	197	Patients with benign and malignant diseases who underwent pancreatic head resection	Subjects randomly sampled from a population-based registry in Sweden	Up to 2 years	None listed	EORTC QLQ-C30 questionnaire	• At initial evaluation, global health was significantly lower in the study population as compared with controls • At the end of the study, QoL was not significantly different from controls • QoL of patients with benign disease was significantly better than that of the patients with malignant disease

73.8 Conclusions

As the understanding of the biology of pancreatic adenocarcinoma improves, long-term survivors after pancreatic resection will increase. Future clinicians and scientists should be aware of the patient-reported outcomes following surgical resection of pancreatic cancer in order to improve the quality of life of this unique patient population.

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
2. Hoffman JP. Status of neoadjuvant therapy for resectable pancreatic cancer. Surg Oncol Clin N Am. 2010;19(2):411–8.
3. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg. 2006;10(9):1199–210; discussion 210–1.
4. Han SS, Jang JY, Kim SW, Kim WH, Lee KU, Park YH. Analysis of long-term survivors after surgical resection for pancreatic cancer. Pancreas. 2006;32(3):271–5.
5. Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg. 2006;10(10):1338–45; discussion 45–6.
6. Ferrone CR, Brennan MF, Gonen M, Coit DG, Fong Y, Chung S, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. J Gastrointest Surg. 2008;12(4):701–6.
7. Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg. 2013;257(4):731–6.
8. Gillen S, Schuster T, Friess H, Kleeff J. Palliative resections versus palliative bypass procedures in pancreatic cancer—a systematic review. Am J Surg. 2012;203(4):496–502.
9. Chandrasegaram MD, Goldstein D, Simes J, Gebski V, Kench JG, Gill AJ, et al. Meta-analysis of radical resection rates and margin assessment in pancreatic cancer. Br J Surg. 2015;102(12):1459–72.
10. Benassai G, Mastrorilli M, Quarto G, Cappiello A, Giani U, Mosella G. Survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas. Chir Ital. 2000;52(3):263–70.
11. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226(3):248–57; discussion 57–60.
12. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993;165(1):68–72; discussion −3.
13. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, Doolas A, et al. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. Am Surg. 1999;65(7):618–23; discussion 23–4.
14. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreatoduodenectomy. Is it an adequate cancer operation. Arch Surg. 1994;129(4):405–12.
15. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg. 1995;221(6):721–31; discussion 31–3.

16. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304(10):1073–81.
17. Michelakos T, Pergolini I, Castillo CF, Honselmann KC, Cai L, Deshpande V, et al. Predictors of resectability and survival in patients with borderline and locally advanced pancreatic cancer who underwent neoadjuvant treatment with FOLFIRINOX. Ann Surg. 2019;269(4):733–40.
18. Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-institutional validation study of the American Joint Commission on Cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg. 2017;265(1):185–91.
19. Ferrone CR, Pieretti-Vanmarcke R, Bloom JP, Zheng H, Szymonifka J, Wargo JA, et al. Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. Surgery. 2012;152(3 Suppl 1):S43–9.
20. Katz MH, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16(4):836–47.
21. Konstantinidis IT, Deshpande V, Zheng H, Wargo JA, Fernandez-del Castillo C, Thayer SP, et al. Does the mechanism of lymph node invasion affect survival in patients with pancreatic ductal adenocarcinoma? J Gastrointest Surg. 2010;14(2):261–7.
22. Honselmann KC, Pergolini I, Castillo CF, Deshpande V, Ting D, Taylor MS, et al. Timing but not patterns of recurrence is different between node-negative and node-positive resected pancreatic cancer. Ann Surg. 2020;272(2):357–65.
23. Huebner M, Kendrick M, Reid-Lombardo KM, Que F, Therneau T, Qin R, et al. Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(5):920–6.
24. Schwarz RE, Smith DD. Extent of lymph node retrieval and pancreatic cancer survival: information from a large US population database. Ann Surg Oncol. 2006;13(9):1189–200.
25. Hellan M, Sun CL, Artinyan A, Mojica-Manosa P, Bhatia S, Ellenhorn JD, et al. The impact of lymph node number on survival in patients with lymph node-negative pancreatic cancer. Pancreas. 2008;37(1):19–24.
26. Wang W, He Y, Wu L, Ye L, Yao L, Tang Z. Efficacy of extended versus standard lymphadenectomy in pancreatoduodenectomy for pancreatic head adenocarcinoma. An update meta-analysis. Pancreatology. 2019;19(8):1074–80.
27. Farnell MB, Aranha GV, Nimura Y, Michelassi F. The role of extended lymphadenectomy for adenocarcinoma of the head of the pancreas: strength of the evidence. J Gastrointest Surg. 2008;12(4):651–6.
28. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–28; discussion 28–30.
29. Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg. 2007;94(3):265–73.
30. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with pancreatic adenocarcinoma: a Surveillance, Epidemiology and End Results (SEER) analysis. Ann Surg Oncol. 2017;24(7):2023–30.
31. Pongprasobchai S, Pannala R, Smyrk TC, Bamlet W, Pitchumoni S, Ougolkov A, et al. Long-term survival and prognostic indicators in small (< or =2 cm) pancreatic cancer. Pancreatology. 2008;8(6):587–92.
32. Mayo SC, Gilson MM, Herman JM, Cameron JL, Nathan H, Edil BH, et al. Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy. J Am Coll Surg. 2012;214(1):33–45.

33. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Fernandez-Del CC. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Surgery. 2015;157(5):881–7.
34. Hank T, Sandini M, Qadan M, Weniger M, Ciprani D, Li A, et al. Diabetes mellitus is associated with unfavorable pathologic features, increased postoperative mortality, and worse long-term survival in resected pancreatic cancer. Pancreatology. 2019;20:125–31.
35. Hallemeier CL, Botros M, Corsini MM, Haddock MG, Gunderson LL, Miller RC. Preoperative CA 19-9 level is an important prognostic factor in patients with pancreatic adenocarcinoma treated with surgical resection and adjuvant concurrent chemoradiotherapy. Am J Clin Oncol. 2011;34(6):567–72.
36. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol. 2006;24(18):2897–902.
37. Berger AC, Garcia M Jr, Hoffman JP, Regine WF, Abrams RA, Safran H, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. J Clin Oncol. 2008;26(36):5918–22.
38. Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol. 2012;23(7):1713–22.
39. Park JK, Paik WH, Ryu JK, Kim YT, Kim YJ, Kim J, et al. Clinical significance and revisiting the meaning of CA 19-9 blood level before and after the treatment of pancreatic ductal adenocarcinoma: analysis of 1,446 patients from the pancreatic cancer cohort in a single institution. PLoS One. 2013;8(11):e78977.
40. Abdel-Misih SR, Hatzaras I, Schmidt C, Saab TB, Klemanski D, Muscarella P, et al. Failure of normalization of CA19-9 following resection for pancreatic cancer is tantamount to metastatic disease. Ann Surg Oncol. 2011;18(4):1116–21.
41. Rieser CJ, Zenati M, Hamad A, Al Abbas AI, Bahary N, Zureikat AH, et al. CA19-9 on postoperative surveillance in pancreatic ductal adenocarcinoma: predicting recurrence and changing prognosis over time. Ann Surg Oncol. 2018;25(12):3483–91.
42. Boone BA, Steve J, Zenati MS, Hogg ME, Singhi AD, Bartlett DL, et al. Serum CA 19-9 response to neoadjuvant therapy is associated with outcome in pancreatic adenocarcinoma. Ann Surg Oncol. 2014;21(13):4351–8.
43. Hadano N, Murakami Y, Uemura K, Hashimoto Y, Kondo N, Nakagawa N, et al. Prognostic value of circulating tumour DNA in patients undergoing curative resection for pancreatic cancer. Br J Cancer. 2016;115(1):59–65.
44. Pietrasz D, Pecuchet N, Garlan F, Didelot A, Dubreuil O, Doat S, et al. Plasma circulating tumor DNA in pancreatic cancer patients is a prognostic marker. Clin Cancer Res. 2017;23(1):116–23.
45. Lee JS, Rhee TM, Pietrasz D, Bachet JB, Laurent-Puig P, Kong SY, et al. Circulating tumor DNA as a prognostic indicator in resectable pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. Sci Rep. 2019;9(1):16971.
46. Mayo SC, Nathan H, Cameron JL, Olino K, Edil BH, Herman JM, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. Cancer. 2012;118(10):2674–81.
47. Malleo G, Maggino L, Ferrone CR, Marchegiani G, Warshaw AL, Lillemoe KD, et al. Reappraising the concept of conditional survival after pancreatectomy for ductal adenocarcinoma: a bi-institutional analysis. Ann Surg. 2020;271(6):1148–55.
48. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120(8):899–903.
49. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319–26.

50. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.
51. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009;100(2):246–50.
52. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389(10073):1011–24.
53. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379(25):2395–406.
54. Heinrich S, Pestalozzi BC, Schafer M, Weber A, Bauerfeind P, Knuth A, et al. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26(15):2526–31.
55. Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol. 2007;14(7):2088–96.
56. Patel M, Hoffe S, Malafa M, Hodul P, Klapman J, Centeno B, et al. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. J Surg Oncol. 2011;104(2):155–61.
57. Sahora K, Kuehrer I, Eisenhut A, Akan B, Koellblinger C, Goetzinger P, et al. NeoGemOx: gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. Surgery. 2011;149(3):311–20.
58. White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol. 2001;8(10):758–65.
59. Festa V, Andriulli A, Valvano MR, Uomo G, Perri F, Andriulli N, et al. Neoadjuvant chemoradiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. JOP. 2013;14(6):618–25.
60. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
61. Vaccaro V, Sperduti I, Milella M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;365(8):768–9; author reply 9.
62. Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2018;4(7):963–9.
63. Murphy JE, Wo JY, Ryan DP, Clark JW, Jiang W, Yeap BY, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. JAMA Oncol. 2019;5(7):1020–7.
64. Ahmad NA, Lewis JD, Ginsberg GG, Haller DG, Morris JB, Williams NN, et al. Long term survival after pancreatic resection for pancreatic adenocarcinoma. Am J Gastroenterol. 2001;96(9):2609–15.
65. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg. 2004;198(5):722–31.
66. Kim YI, Song KB, Lee YJ, Park KM, Hwang DW, Lee JH, et al. Management of isolated recurrence after surgery for pancreatic adenocarcinoma. Br J Surg. 2019;106(7):898–909.
67. Schniewind B, Bestmann B, Henne-Bruns D, Faendrich F, Kremer B, Kuechler T. Quality of life after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head. Br J Surg. 2006;93(9):1099–107.
68. Cloyd JM, Tran Cao HS, Petzel MQ, Denbo JW, Parker NH, Nogueras-Gonzalez GM, et al. Impact of pancreatectomy on long-term patient-reported symptoms and quality of life in recurrence-free survivors of pancreatic and periampullary neoplasms. J Surg Oncol. 2017;115(2):144–50.

69. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg. 2000;231(6):890–8.
70. Pezzilli R, Falconi M, Zerbi A, Casadei R, Valli L, Varale R, et al. Clinical and patient-reported outcomes after pancreatoduodenectomy for different diseases: a follow-up study. Pancreas. 2011;40(6):938–45.
71. Fong ZV, Alvino DM, Castillo CF, Nipp RD, Traeger LN, Ruddy M, et al. Health-related quality of life and functional outcomes in 5-year survivors after pancreaticoduodenectomy. Ann Surg. 2017;266(4):685–92.
72. Tung S, Davis LE, Hallet J, Mavros MN, Mahar AL, Bubis LD, et al. Population-level symptom assessment following pancreaticoduodenectomy for adenocarcinoma. JAMA Surg. 2019;154:e193348.
73. Ferrell BR, Wisdom C, Wenzl C. Quality of life as an outcome variable in the management of cancer pain. Cancer. 1989;63(11 Suppl):2321–7

Chapter 74
Patterns of Recurrence After Surgery for Pancreatic Cancer

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Take Home Messages

- Disease recurrence occurs in up to 80–90% of patients after resection of pancreatic cancer and is the main cause of disease-specific mortality.
- The main recurrence patterns following resection for pancreatic cancer include hepatic metastases, peritoneal carcinomatosis, locoregional recurrence and pulmonary metastases.

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- More than 75% of recurrences occur at distant sites, demonstrating that most patients with pancreatic cancer should be presumed to have systemic disease at the time of resection.
- Specific recurrence locations have different predictive factors and demonstrate distinct recurrence-free survival rates, supporting the hypothesis that unique biological heterogeneity exists among pancreatic cancer leading to distinct recurrence patterns.
- Timing of recurrence impacts subsequent prognosis, with a recurrence-free interval of 12 months as the optimal threshold for differentiating between early and late recurrence.

Pearls and Pitfalls

- Hepatic recurrence, peritoneal carcinomatosis and multiple-site recurrence occur early and are associated with relatively limited overall survival.
- Isolated local or pulmonary recurrence seem to be associated with relatively favorable outcomes, possibly warranting more aggressive and/or localized additional treatment.
- The length of recurrence-free survival could be a clinically useful surrogate for appreciating pancreatic cancer behaviour.
- Data on the pattern and timing of pancreatic cancer recurrence vary significantly and are often contradictory, probably due to the retrospective nature of the performed studies and differences in follow-up strategies.
- The vast majority of studies on recurrence only provide information on the first site of recurrence, whilst further disease progression is not accounted for.
- Relatively little is known about recurrence patterns and biological behaviour following the new paradigm of neoadjuvant therapy followed by resection of pancreatic cancer.

Future Perspectives

- Genetic analyses of both primary tumours and metastases are needed to understand the underlying biological mechanisms that might lead to different organ-specific recurrences and their associated survival.
- Prospective studies are needed that focus on the development of patient-tailored multimodality treatment approaches that take into account the diverse biological behaviours of pancreatic cancer recurrence.
- Improved understanding of the prognostic impact of recurrence characteristics at the time of recurrence would help select patients who could benefit from additional treatment.

74.1 Introduction

Radical resection of localized pancreatic cancer, combined with (neo)adjuvant systemic therapy, provides patients with the best chance of long-term survival. However, even after completion of curative-intent resection and systemic therapy, disease recurrence is common and the foremost cause of disease-specific mortality [1]. As a result, less than 4% of resected pancreatic cancer patients continue to live 10 years or more [2]. In 2018, the PRODIGE-24 trial published exciting novel results of adjuvant treatment with modified FOLFIRINOX, achieving an unprecedented median survival of 54 months [3]. Yet, despite the encouraging survival, more than 50% of patients in the modified FOLFIRINOX study group, and more than 70% in the gemcitabine group developed disease recurrence. As the data of this trial remain immature, with 61% of all patients being alive at the time of analysis, this number of patients with recurrence will undoubtedly continue to rise.

Patients undergoing curative-intent resection of pancreatic cancer are theoretically rendered free of clinical disease at a defined time point. Thus, the natural pattern and rate of recurrence can be assessed based on this consistent frame of reference, helping understand the heterogeneity in behaviour of pancreatic cancer. This heterogeneity is evident, as diverse patterns and timing of recurrence exist. For example, while the majority of patients present with systemic disease or progress to develop systemic disease, a significant proportion of patients will develop isolated local recurrence [4]. Furthermore, even among the patients who develop systemic disease, metastatic spread will in some cases be limited to the liver, lung, or peritoneum.

As the PRODIGE-24 trial demonstrates, disease recurrence remains the major barrier to curing patients with resected pancreatic cancer. An accurate understanding of treatment failure after seemingly successful surgery is essential in the pursuit of novel therapies that can improve outcomes for pancreatic cancer patients. Furthermore, detailed awareness of the timing of disease recurrence and the factors predicting specific recurrence patterns can potentially help guide a more personalized approach to postoperative surveillance and treatment. For instance, knowledge on the prognostic impact of recurrence can assist both patients and physicians when discussing the balance between quality of life and further treatment options. Therefore, the current chapter aims to provide an extensive comprehension of multiple aspects of recurrence after pancreatectomy for pancreatic cancer.

74.2 Patterns of Pancreatic Cancer Recurrence

74.2.1 Pathways of Metastatic Spread

Patients who present with primary metastatic pancreatic cancer can provide insight in the different pathways of disease dissemination, which is important to understand the patterns of recurrence after surgery for localized disease. Cancer of the pancreas is situated deep in the retroperitoneum and typically infiltrates a network of crucial arteries, veins, and nerves that supply or drain the liver, spleen, stomach, and large

and small bowel [5]. Multiple autopsy series demonstrate that hepatic and (retro) peritoneal metastases generally constitute the two primary modes of metastatic spread in pancreatic cancer, with hepatic metastases occurring more frequently [6–9]. Since essentially all veins draining the pancreas flow into the portal system, it is unsurprising that hematogenous spread primarily occurs to the liver (Fig. 74.1a) [10]. On the other hand, most local retroperitoneal and peritoneal dissemination is believed to be caused by invasion of neural and lymphatic pathways, and through loose connective tissue infiltration around the superior mesenteric artery (Fig. 74.1b, c) [7, 11].

Metastases outside the abdominal cavity occur less frequently but are not uncommon. Extra-abdominal spread predominantly occurs to the lungs and is believed to be caused by hematogenous seeding via routes that circumvent the liver, for instance through collateral vessels caused by portal vein or splenic vein obstruction, thus bypassing the portal systemic circulation (Fig. 74.1d) [10]. Additionally, several potential lymphatic routes have been described for pulmonary metastases from pancreatic cancer; (1) through pleural lymphatics along connective tissue septa and into the alveolar spaces and bronchial walls, (2) through retrograde lymphatic invasion of the lung from the tracheobronchial or mediastinal glands, and (3) through involvement of metastatic lymph nodes of the venous angle [12, 13].

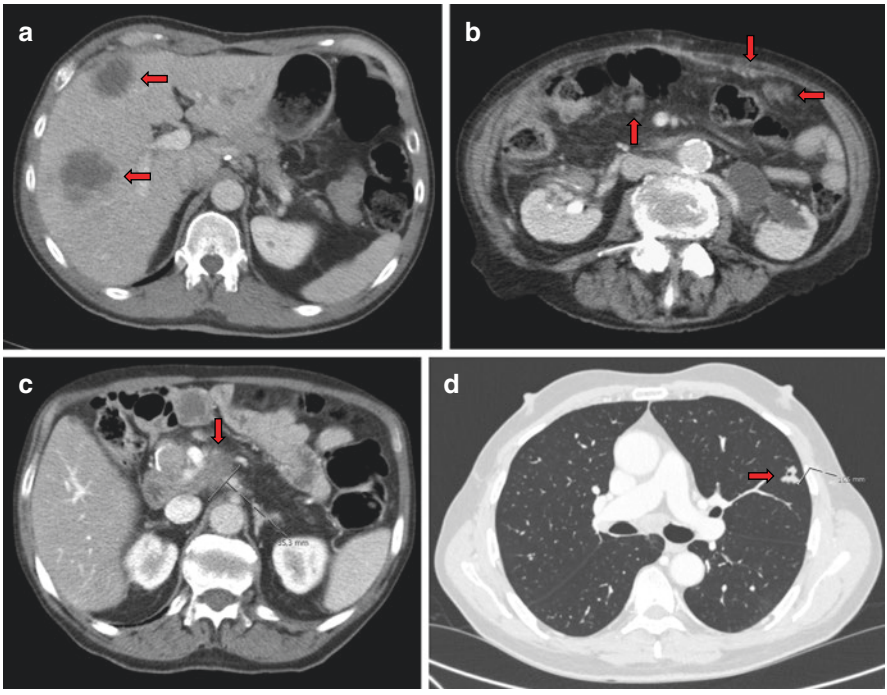

Fig. 74.1 Transversal CT imaging of different patients showing various pancreatic cancer recurrence locations. (**a**) hepatic recurrence, (**b**) peritoneal carcinomatosis, (**c**) local recurrence, and (**d**) pulmonary recurrence

74.2.2 Patterns of Recurrence

Historical literature on patterns and timing of disease recurrence after curative-intent surgery for pancreatic cancer varies significantly, possibly due to smaller sample sizes and differences in follow-up strategies. A recent and relatively large study that focused on the patterns and timing of recurrence includes 692 patients who underwent upfront pancreatectomy at the Johns Hopkins Hospital [4]. In this study, 77% of resected patients experienced disease recurrence after a median recurrence-free interval of 12 months. Mirroring the described metastatic pathways in primary metastatic pancreatic cancer, the most common manifestations of pancreatic cancer recurrence was multiple-site (33%; including peritoneal carcinomatosis) and liver-only (25%), followed by local-only (24%), and lung-only (15%) recurrence (Fig. 74.2) [4]. Of patients with recurrence, 58% first recurred at isolated distant sites while an additional 19% had both a local and distant site as first recurrence location. In these patients with local and distant recurrence, liver and lung lesions were found most often in combination with local recurrence. Intra-abdominal recurrence occurred solitarily in 77% patients and together with extra-abdominal

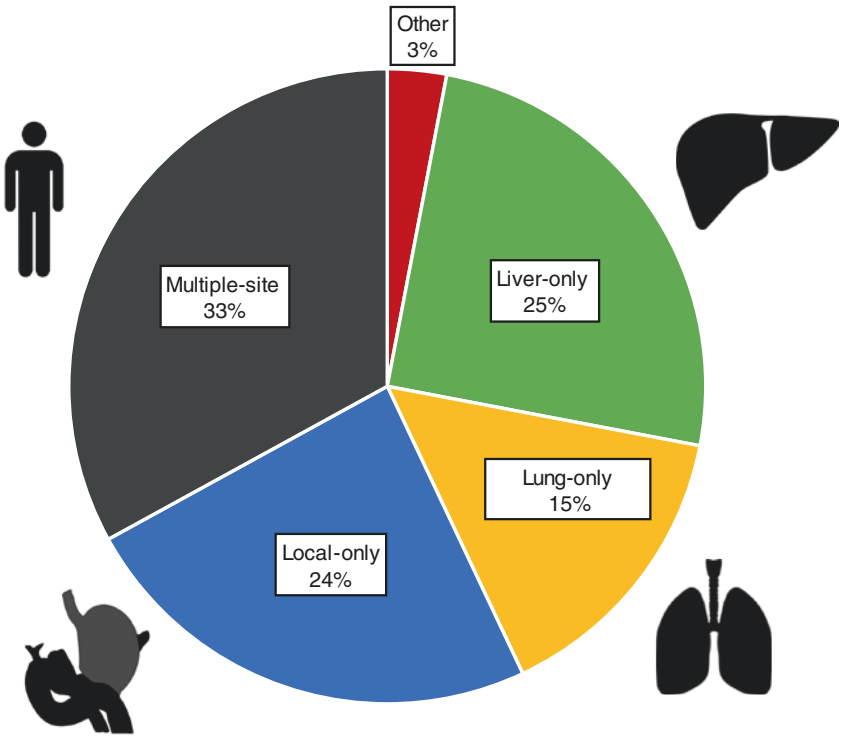

Fig. 74.2 Distribution of recurrence patterns after resection of pancreatic cancer. (Based on data from Ref. (4))

recurrence in 6% of patients. Solitary extra-abdominal recurrence was less common (18%) and occurred predominantly in the lung (15%). Other extra-abdominal recurrences were rare (3%) and were located in osseous structures, the brain, supraclavicular lymph nodes, the groin, thigh muscle, and the skin.

A systematic review with a meta-analysis of recurrence patterns that included 89 studies with 17.313 patient undergoing pancreatic cancer resection found weighted median recurrence rates of 27% for liver recurrence, 21% for locoregional recurrence, 14% for peritoneal dissemination, and 11% for lung recurrence [14]. The recurrence location rates of the Johns Hopkins series and pooled rates of this meta-analysis are remarkably similar, suggesting these recurrence patterns are an accurate representation of the true pattern of recurrence after resection for pancreatic cancer.

For isolated local recurrence, the described rates in clinical studies are remarkably higher (>20%) than those found in autopsy studies (<10%) of patients with recurrent disease after resection [7, 8, 15, 16]. These findings are presumably indicative of the advanced disease stage at which the autopsies were performed. It remains unclear if distant spread originated from the local recurrence, had migrated to distant sites before resection, or migrated intraoperatively as a result of surgical manipulation. It could be argued that patients who experience a long interval between local recurrence and secondary distant metastases are likely to have metastases originating from their local recurrence. However, given the fact that more than 75% of initial recurrences seem to occur at a distant site, it is unlikely that local recurrence give rise to subsequent distant metastases in the majority of patients. Consequently, most patients with pancreatic cancer should be presumed to have systemic disease at the time of resection.

Most available evidence on recurrence patterns is based on patients undergoing upfront pancreatectomy without neoadjuvant treatment. Neoadjuvant therapy followed by pancreatectomy for both borderline resectable and locally advanced pancreatic cancer is a fast-growing paradigm in pancreatic cancer care [17, 18]. Few studies have assessed disease recurrence after neoadjuvant therapy followed by resection of pancreatic cancer as a primary outcome of interest. Furthermore, recurrence rates reported in these few studies differ considerably. For instance, seven large contemporary studies that included data on recurrence after post-neoadjuvant resection of borderline resectable and/or locally advanced disease reported relatively low overall recurrence rates ranging from 38% to 65% [19, 20]. However, one of the first prospective randomized trials found a recurrence rate of up to 88% in 17 borderline resectable patients undergoing post-neoadjuvant resection [21]. Similarly, a large retrospective series of borderline resectable and/or locally advanced reported a recurrence rate of 82% [20]. In this study, more than 70% of recurrences occurred at distant sites, suggesting that despite a radiographic progression-free period leading to resection, viable micrometastatic disease can persist after systemic neoadjuvant treatment. Even in patients with a pathologic complete response after neoadjuvant therapy, more than 50% develop locoregional or distant recurrence [22, 23, 24]. Yet, neoadjuvant therapy has been encouragingly associated with a decreased rate of hepatic metastases, a finding also reported in a recent

meta-analysis on recurrence patterns after neoadjuvant therapy and resection [19, 20]. Unfortunately, the PREOPANC trial published in 2020 on neoadjuvant treatment and resection of (borderline) resectable pancreatic cancer did not report specific recurrence data [18]. Hopefully, future prospective clinical trials on neoadjuvant therapy for localized disease, such as the ALLIANCE trial, will provide more accurate recurrence data [25].

74.3 Predictors of Pancreatic Cancer Recurrence

Prognostic factors for survival outcomes after surgical resection of pancreatic cancer have been studied extensively [26, 27]. Well-known predictors of survival include both clinical characteristics (patient comorbidities, operative complications, peri-operative CA 19-9 levels, adjuvant status) and pathologic features (tumour size and nodal status (TNM staging [28]), tumour differentiation, margin status, microscopic perineural and lymphovascular invasion) [1, 28–30]. As pancreatic cancer recurrence is the major reason for disease-specific mortality, many of the reported risk factors for decreased survival are also predictive of an increased likelihood of recurrence [31–33].

Evidence is starting to emerge that distinctive clinicopathologic features correlate with specific patterns of recurrence (Table 74.1) [4, 14, 34–36]. For instance, adjuvant therapy following resection reduces the likelihood of both local and distant recurrence [4, 14, 33, 36]. High positive lymph node ratio status and/or N2 status are consistently reported as strong predictors for distant recurrence [4, 36]. Additionally, R1- and R2-resection (defined as distance of tumour cells to the closest resection $\leq$1 mm (R1) and gross disease at the margins (R2)) is predictably associated with locoregional recurrence [4, 14, 37]. Microscopic lymphovascular invasion and a positive lymph node ratio >0.2 have been identified as independent predictors for pulmonary recurrence [4]. Lastly, poor tumour differentiation has been established as a specific predictor for hepatic recurrence [38, 39]. Although poor tumour differentiation has been recognized previously as an indicator of poor prognosis, the exact relation remains unclear [40, 41]. An intriguing proposed hypothesis argues that several molecules that are expressed at high levels in undifferentiated tumours, including epidermal growth factor receptor, E-cadherin, and laminin γ-chain, may enhance the ability of pancreatic cancer to metastasize to the liver [4, 34].

Carbohydrate antigen (CA) 19-9 is the most studied and well-known biomarker for pancreatic cancer [42]. Multiple reports have established the association between elevated pre- and postoperative CA 19-9 levels and decreased post-pancreatectomy survival [43]. However, far fewer studies have focused on the correlation between CA 19–9 and recurrence. Furthermore, there is currently no consensus regarding the CA 19-9 threshold for prediction of recurrence, with varying pre-operative levels between 50 and 500 U/mL being advocated [44–46]. Also, CA 19-9 can be falsely elevated in extra-pancreatic malignancies and benign conditions [43]. In research settings, liquid biopsies show promise as a novel biomarker for improving the

Table 74.1 Overview of independent predictive factors for specific recurrence patterns of pancreatic cancer

	Study			
Recurrence pattern	Shibata et al. (2005) Cohort study	Groot et al. (2018) Cohort study	Tanaka et al. (2019) Meta-analysis	Jones et al. (2019) ESPAC-4 RCT
Liver-only	Poor Tdiff (OR 7.43)	Tsize in cm (HR 1.13) Poor Tdiff (HR 2.48) LNR >0.2 (HR 1.49)	Moderate/poor Tdiff (OR 4.15)	N.A.
Multiple-site	N.A.	Poor Tdiff (HR 1.72) LNR >0.2 (HR 2.65)	N.A.	N.A.
Distant-only	N.A.	N.A.	N.A.	Moderate/Well Tdiff (HR 0.60) Postoperative CA 19-9 (HR 1.32) N2 (HR 2.16)
Local-only	None	R1 margin (HR 2.46) CHRT (HR 0.64)	NAT (OR 0.32) CHT (OR 0.65) R2 margin (OR 3.18)	CHT (HR 0.77) N1 (HR 1.76) N2 (HR 2.81)
Lung-only	N.A.	PVI (HR 1.67) LNR >0.2 (HR 3.30)	None	N.A.
Local + distant	N.A.	PVI (HR 1.73) LNR >0.2 (HR 2.10) CHT (HR 0.33) CHRT (HR 0.26)	N.A.	N.A.
Peritoneal carcinomatosis	Portal vein invasion (OR 3.97)	N.A.	R2 margin (OR 2.21) PNI (OR 5.19) Pos. peritoneal lavage cytology (OR 5.29)	N.A.
Other	N.A.	R1 margin (HR 4.01) LNR >0.2 (HR 3.15)	N.A.	N.A.

CA carbohydrate antigen, *CHT* adjuvant chemotherapy, *CHRT* adjuvant chemoradiotherapy, *HR* hazard ratio, *LNR* positive lymph node ratio, *N.A.* not applicable, *N1* 1–3 positive lymph nodes, *N2* >3 positive lymph nodes, *NAT* neoadjuvant treatment, *OR* odds ratio, *PNI* microscopic perineural invasion, *Pos.* positive, *PVI* microscopic perivascular invasion, *R1 margin* ≤1 mm, *R2* gross disease at margins, *RCT* randomized controlled trial, *Tdiff* tumor differentiation, *Tsize* tumor size

perioperative prediction of pancreatic cancer recurrence. For instance, multiple prospective studies demonstrate that pre- and post-operative detection of circulating tumour cells and DNA are independent predictors for the development of recurrence [47–50]. Currently however, there is insufficient evidence of clinical validity and utility for the majority of liquid biopsy test to be used outside of clinical studies [51].

74.4 Timing and Implications of Pancreatic Cancer Recurrence

74.4.1 Timing of Recurrence

Pancreatic cancer is a highly heterogeneous disease. This is not only expressed in the various described recurrence patterns, but also in the differences in timing of disease recurrence and the resulting implications on overall survival (Fig. 74.3). For instance, hepatic recurrence is responsible for about half of recurrences in the first 6 months, while local and lung-only recurrence combine for more than half of all recurrences occurring after 2 years post-pancreatectomy [4]. Additionally, 97% of

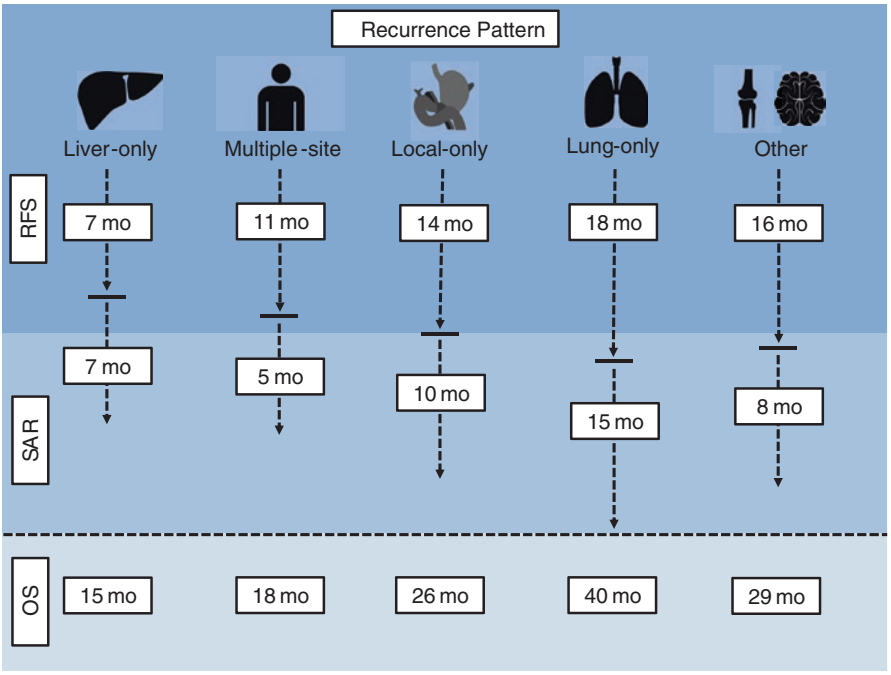

Fig. 74.3 Different recurrence patterns of pancreatic cancer with associated survival. Distinct median recurrence-free survival (RFS), survival after recurrence (SAR) and overall survival (OS) in months (mo), based on data from Ref. (56)

all observed recurrences in the Johns Hopkins series had occurred by 5 years after resection, highlighting the difficulty of curing pancreatic cancer [4]. Furthermore, of the patients who were free of recurrence after 5 years, up to 20% went on to develop either local (60%) or distant (40%) recurrence, indicating that prolonged recurrence-free survival unfortunately does not equal cure.

Several studies have described significant differences in the timing of recurrence based on specific recurrence locations [4, 31, 52–56]. In general, these studies conclude that isolated local recurrence and lung recurrence occur relatively late, after a median recurrence-free interval exceeding 12 months. On the other hand, peritoneal dissemination, liver-only and multiple-site recurrence tend to occur early, with described median recurrence-free intervals of just 6 months. More specifically, in their meta-analysis, Tanaka et al. reported median-free survival intervals of 13 months for local-only, 12 months for lung-only and 7 months for liver-only recurrence [14]. Lastly, patient with peritoneal carcinomatosis had a median recurrence-free interval of 9 months.

74.4.2 Implications of Recurrence on Survival

Both timing and patterns of recurrence have been shown to have implications on survival after recurrence and thus overall survival after pancreatectomy. Two studies that investigated the prognostic impact of timing of recurrence imply that the optimal cut-off value to differentiate between "early" and "late" recurrence, based on subsequent prognosis, is a recurrence-free interval of 12 months [57, 58]. Specifically, one study showed that patients who recurred within 12 months had a post-recurrence survival of 6 months compared with a post-recurrence survival of 11 months for patients with late recurrence ($P < 0.001$) [58]. This resulted in a significantly longer median overall survival of 35 months for patients with "late" recurrence when compared to just 13 months for patients with "early" recurrence ($P < 0.001$). The fact that patients with a prolonged recurrence-free interval after surgery also tend to live longer after they recurred, may suggest favourable tumour biology. Conversely, more aggressive tumour biology may lead to shorter recurrence-free survival followed by a more rapid progression to death. In this way, timing of recurrence could be a clinically useful surrogate for appreciating pancreatic cancer behaviour.

Relatively few studies have focused on the impact of recurrence patterns on survival after recurrence and overall survival. Most studies showed significant correlations between patterns of recurrence and survival outcomes, supporting the hypothesis that unique biological behaviours exist among pancreatic cancer [31, 52, 53, 56, 59–63]. The impact of recurrence location on survival after recurrence more or less mirrors the unique recurrence-free survival intervals of the specific recurrence sites (Fig. 74.3) [56]. For instance, liver-only recurrence is associated with both relatively short recurrence-free survival (median 7 months) and short survival after recurrence (median 7 months), resulting in a median overall survival of just 15 months after pancreatectomy. On the other hand, local-only and lung-only

recurrence, which generally occur later, were associated with significantly longer post-recurrence survival of 10 and 15 months, respectively. A pooled meta-analysis by Tanaka et al. reported median post-recurrence and overall survival of 8 and 12 months for locoregional recurrence, 6 and 15 months for liver recurrence, 12 and 30 months for lung recurrence, and 4 and 14 months for peritoneal dissemination [14].

A complete understanding of why local and pulmonary recurrence are associated with relatively favorable survival outcomes remains elusive. The favorable prognosis for patients with isolated local recurrence might be a consequence of the fact that local recurrence can originate from microscopic residual disease in the remnant pancreas that has not gone through the process of hematogenous dissemination [64]. For pulmonary recurrence, one plausible theory assumes that the large capacity of the lungs allows patients to endure a greater metastatic tumour burden leading to extended survival [61].

74.5 Future Research

Disease recurrence unfortunately remains common, and often marks a critical and emotional time point in the care of patients with resected pancreatic cancer [65]. The different recurrence patterns with associated distinct timing, predictors and survival implications presented in this chapter support the hypothesis that unique biological differences exist among primary tumours. To date, the underlying biological mechanisms causing different pancreatic cancer recurrence patterns and associated survival outcomes remain unexplained. It is plausible that both the first recurrence site and tumour aggressiveness are determined by common underlying biologic pathways [66]. Future genetic analyses of both primary tumours and metastases might elucidate if distinct genetic signatures lead to different organ-specific recurrences. This possibility seems likely, as molecular profiling has been shown to predict cancer recurrence in prostate, stomach, and liver cancer [67–69].

Currently, *SMAD4* status is one example of how underlying genetic status can correlate with biological behaviour in pancreatic cancer: cancers not expressing *SMAD4* are associated with a high metastatic burden, while tumours with intact *SMAD4* tend to remain localized [16]. Evidently, the promise of combining clinical factors with genetic signatures to predict recurrence patterns would have important implications for improving post-operative follow-up strategies and the quest toward personalized medicine for patients with pancreatic cancer [4]. Future studies might reveal genetic signatures associated with recurrence patterns, possibly contributing to prognosis stratification, targets of treatment, and a more patient-tailored approach for patients with pancreatic cancer.

Apart from translational research efforts, future research should focus on the management of patients with recurrence. Treatment of recurrent pancreatic cancer is less well established as it is for other stages of pancreatic cancer [70, 71]. The different prognostic implications of the patterns and timing of recurrence can

provide future studies with a basis to develop patient-tailored multimodality treatment approaches that take into account the diverse behaviours of recurrent disease. Particularly isolated local or pulmonary recurrence seem to be associated with relatively favorable outcomes. The apparent less aggressive tumour biology and slower growing tendency might warrant more aggressive and/or localized additional treatment. Initial small studies on metastasectomy for pulmonary metastases, and stereotactic body radiation therapy and/or even re-resection for isolated local recurrence, have shown promising results [13, 72–74]. However, future well-designed prospective studies on the treatment of recurrence are needed to prove that extended survival of patients undergoing additional treatment for recurrence is not based on selection bias alone.

Importantly, future research on pancreatic cancer recurrence should account for the prognostic impact of other patient and tumour characteristics at the time of recurrence diagnosis. Little is currently known about these other potential predictive factors, such as patient fitness and age, symptoms, tumour burden and CA 19-9 levels. Furthermore, almost all studies on recurrence only provide information on the first site of recurrence, whilst further disease progression is not accounted for. Additional data on secondary disease spread might potentially reveal associations not currently appreciated and help better define the arc of the disease. Improved prognostication has the potential to greatly aid clinicians in the counselling of patients with disease recurrence whom are often facing challenging clinical choices between quality of life and further treatment options.

74.6 Conclusion

Disease recurrence occurs in up to 80–90% of patients after resection of pancreatic cancer and is the main cause of disease-specific mortality. The main recurrence patterns include hepatic metastases, peritoneal carcinomatosis, locoregional recurrence and pulmonary metastases. As 75% of recurrences occur at distant sites, most patients with pancreatic cancer should be presumed to have systemic disease at the time of resection. The different recurrence patterns exhibit different behaviours that result in distinct predictive factors, timing of recurrence and survival implications. Future studies that take into account the diverse biological behaviours of pancreatic cancer recurrence could contribute to improved prognosis stratification, new targets of treatment, and a more patient-tailored approach for patients with pancreatic cancer.

References

1. Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, et al. Recent progress in pancreatic cancer. CA Cancer J Clin. 2013;63:318–48.
2. Paniccia A, Hosokawa P, Henderson W, Schulick RD, Edil BH, McCarter MD, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. JAMA Surg. 2015;150:701–10.

3. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018;379:2395–406.
4. Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, et al. Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg. 2018;267:936–45.
5. Cannistrà M, Ruggiero M, Zullo A, Serafini S, Grande R, Nardo B. Metastases of pancreatic adenocarcinoma: a systematic review of literature and a new functional concept. Int J Surg. 2015;21:S15–21.
6. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. Ann Surg. 1984;199:418–25.
7. Kayahara M, Nagakawa T, Ueno K, Ohta T, Takeda T, Miyazaki I. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer. 1993;72:2118–23.
8. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: correlations of a clinical trial. Int J Radiat Oncol Biol Phys. 1993;27:831–4.
9. Blastik M, Plavecz E, Zalatnai A. Pancreatic carcinomas in a 60-year, institute-based autopsy material with special emphasis of metastatic pattern. Pancreas. 2011;40:478–80.
10. Kamisawa T, Isawa T, Koike M, Tsuruta K, Okamoto A. Hematogenous metastases of pancreatic ductal carcinoma. Pancreas. 1995;11:345–9.
11. Nagai H, Kuroda A, Morioka Y. Lymphatic and local spread of T1 and T2 pancreatic cancer. A study of autopsy material. Ann Surg. 1986;204:65–71.
12. Lisa JR, Trinidad S, Rosenblatt MB. Pulmonary manifestations of carcinoma of the pancreas. Cancer. 1964;17:395–401.
13. Groot VP, Blair AB, Gemenetzis G, Ding D, Burkhart RA, van Oosten AF, et al. Isolated pulmonary recurrence after resection of pancreatic cancer: the effect of patient factors and treatment modalities on survival. HPB (Oxford). 2019;21:998–1008.
14. Tanaka M, Mihaljevic AL, Probst P, Heckler M, Klaiber U, Heger U, et al. Meta-analysis of recurrence pattern after resection for pancreatic cancer. Br J Surg. 2019;106:1590–601.
15. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. J Gastrointest Surg. 2006;10:511–8.
16. Iacobuzio-donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009;27:1806–13.
17. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg. 2019;270:340–7.
18. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020;38:1763–73.
19. Schorn S, Demir IE, Samm N, Scheufele F, Calavrezos L, Sargut M, et al. Meta-analysis of the impact of neoadjuvant therapy on patterns of recurrence in pancreatic ductal adenocarcinoma. BJS Open. 2018;2:52–61.
20. Groot VP, Blair AB, Gemenetzis G, Ding D, Burkhart RA, Yu J, et al. Recurrence after neoadjuvant therapy and resection of borderline resectable and locally advanced pancreatic cancer. Eur J Surg Oncol. 2019;45:1674–83.
21. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: a prospective, randomized, open-label, multicenter phase 2/3 trial. Ann Surg. 2018;268:215–22.
22. Blair AB, Yin L-D, Pu N, Yu J, Groot VP, Rozich NS, et al. Detection, Treatment, and Survival of Pancreatic Cancer Recurrence in the Netherlands A Nationwide Analysis. Ann Surg. November 2019 [Epub Ahead of Print]. https://doi.org/10.1097/SLA.0000000000003570.

23. Hashemi-Sadraei N, Gbolahan OB, Salfity H, O'Neil B, House MG, Shahda S. Clinical characteristics of patients experiencing pathologic complete response following neoadjuvant therapy for borderline resectable/locally advanced pancreatic adenocarcinoma. Am J Clin Oncol. 2018;41:982–5.
24. He J, Blair AB, Groot VP, Javed AA, Burkhart RA, Gemenetzis G, et al. Is a pathological complete response following neoadjuvant chemoradiation associated with prolonged survival in patients with pancreatic cancer? Ann Surg. 2018;268:1–8.
25. Katz MH, Ou FS, Herman JM, Ahmad SA, Wolpin B, Marsh R, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. BMC Cancer. 2017;17:505.
26. Strijker M, Chen JW, Mungroop TH, Jamieson NB, van Eijck CH, Steyerberg EW, et al. Systematic review of clinical prediction models for survival after surgery for resectable pancreatic cancer. Br J Surg. 2019;106:342–54.
27. van Roessel S, Strijker M, Steyerberg EW, Groen JV, Mieog JS, Groot VP, et al. International validation and update of the Amsterdam model for prediction of survival after pancreatoduodenectomy for pancreatic cancer. Eur J Surg Oncol. 2020;46:796–803.
28. Van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, De Pastena M, et al. International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg. 2018;153:e183617.
29. Wu W, He J, Cameron JL, Makary M, Soares K, Ahuja N, et al. The impact of postoperative complications on the administration of adjuvant therapy following pancreaticoduodenectomy for adenocarcinoma. Ann Surg Oncol. 2014;21:2873–81.
30. Oba A, Croce C, Hosokawa P, Meguid C, Torphy RJ, Al-Musawi MH, et al. Prognosis based definition of resectability in pancreatic cancer. Ann Surg. 2020; https://doi.org/10.1097/SLA.0000000000003859.
31. Tani M, Kawai M, Miyazawa M, Hirono S, Ina S, Nishioka R, et al. Liver metastasis as an initial recurrence has no impact on the survival of patients with resectable pancreatic adenocarcinoma. Langenbecks Arch Surg. 2009;394:249–53.
32. Asiyanbola B, Gleisner A, Herman JM, Choti MA, Wolfgang CL, Swartz M, et al. Determining pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-flurouracil-based chemoradiation therapy: effect of number of metastatic lymph nodes and lymph node ratio. J Gastrointest Surg. 2009;13:752–9.
33. Parikh AA, Maiga A, Bentrem D, Squires MH, Kooby DA, Maithel SK, et al. Adjuvant therapy in pancreas cancer: does it influence patterns of recurrence? J Am Coll Surg. 2016;222:448–56.
34. Shibata K, Matsumoto T, Yada K, Sasaki A, Ohta M, Kitano S. Factors predicting recurrence after resection of pancreatic ductal carcinoma. Pancreas. 2005;31:69–73.
35. Kovač JD, Mayer P, Hackert T, Klauss M. The time to and type of pancreatic cancer recurrence after surgical resection: is prediction possible? Acad Radiol. 2019;26:775–81. http://www.ncbi.nlm.nih.gov/pubmed/30254003.
36. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of recurrence after resection of pancreatic ductal adenocarcinoma: a secondary analysis of the ESPAC-4 randomized adjuvant chemotherapy trial. JAMA Surg. 2019;154:1038–48.
37. Sugiura T, Uesaka K, Mihara K, Sasaki K, Kanemoto H, Mizuno T, et al. Margin status, recurrence pattern, and prognosis after resection of pancreatic cancer. Surgery. 2013;154:1078–86.
38. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg. 2003;237:74–85.
39. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg. 2004;198:722–31.

40. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg. 2000;4:567–79.
41. Kuhlmann KF, De Castro SM, Wesseling JG, Ten Kate FJ, Offerhaus GJ, Busch OR, et al. Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients. Eur J Cancer. 2004;40:549–58.
42. Daamen LA, Groot VP, Heerkens HD, Intven MPW, van Santvoort HC, Molenaar IQ. Systematic review on the role of serum tumor markers in the detection of recurrent pancreatic cancer. HPB (Oxford). 2018;20:297–304.
43. Poruk KE, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, et al. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. Curr Mol Med. 2013;13:340–451.
44. Kim TH, Han SS, Park SJ, Lee WJ, Woo SM, Yoo T, et al. CA 19-9 level as indicator of early distant metastasis and therapeutic selection in resected pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;81:e743–8.
45. Sugiura T, Uesaka K, Kanemoto H, Mizuno T, Sasaki K, Furukawa H, et al. Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16:977–85.
46. Nishio K, Kimura K, Amano R, Yamazoe S, Ohrira G, Nakata B, et al. Preoperative predictors for early recurrence of resectable pancreatic cancer. World J Surg Oncol. 2017 Jan;15:16.
47. Hadano N, Murakami Y, Uemura K, Hashimoto Y, Kondo N, Nakagawa N, et al. Prognostic value of circulating tumour DNA in patients undergoing curative resection for pancreatic cancer. Br J Cancer. 2016;115:59–65.
48. Bernard V, Kim DU, San Lucas FA, Castillo J, Allenson K, Mulu FC, et al. Circulating nucleic acids associate with outcomes of patients with pancreatic cancer. Gastroenterology. 2018;156:108–18.
49. Gemenetzis G, Groot VP, Yu J, Ding D, Teinor JA, Javed AA, et al. Circulating tumor cells dynamics in pancreatic adenocarcinoma correlate with disease status. Ann Surg. 2018;268:408–20.
50. Groot VP, Mosier S, Javed AA, Teinor JA, Gemenetzis G, Ding D, et al. Circulating tumor DNA as a clinical test in resected pancreatic cancer. Clin Cancer Res. 2019;25:4973–84.
51. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018;36:1631–41.
52. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg. 1997;21:195–200.
53. Van den Broeck A, Sergeant G, Ectors N, Van Steenbergen W, Aerts R, Topal B. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. Eur J Surg Oncol. 2009;35:600–4.
54. Suenaga M, Fujii T, Kanda M, Takami H, Okumura N, Inokawa Y, et al. Pattern of first recurrent lesions in pancreatic cancer: hepatic relapse is associated with dismal prognosis and portal vein invasion. Hepatogastroenterology. 2014;61:1756–61.
55. Zhang Y, Frampton AE, Kyriakides C, Bong JJ, Habib N, Ahmad R, et al. Loco-recurrence after resection for ductal adenocarcinoma of the pancreas: predictors and implications for adjuvant chemoradiotherapy. J Cancer Res Clin Oncol. 2012;138:1063–71.
56. Groot VP, Gemenetzis G, Blair AB, Ding D, Javed AA, Burkhart RA, et al. Implications of the pattern of disease recurrence on survival following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2018;25:2475–83.
57. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. Optimal duration of the early and late recurrence of pancreatic cancer after pancreatectomy based on the difference in the prognosis. Pancreatology. 2014;14:524–9.

58. Groot VP, Gemenetzis G, Blair AB, Rivero-Soto RJ, Yu J, Javed AA, et al. Defining and predicting early recurrence in 957 patients with resected pancreatic ductal adenocarcinoma. Ann Surg. 2019;269:1154–62.
59. Papavasiliou P, Hoffman JP, Cohen SJ, Meyer JE, Watson JC, Chun YS. Impact of preoperative therapy on patterns of recurrence in pancreatic cancer. HPB (Oxford). 2014;16:34–9.
60. Lovecek M, Skalicky P, Chudacek J, Szkorupa M, Svebisova H, Lemstrova R, et al. Different clinical presentations of metachronous pulmonary metastases after resection of pancreatic ductal adenocarcinoma: retrospective study and review of the literature. World J Gastroenterol. 2017;23:6420–8.
61. Zheng B, Ohuchida K, Yan Z, Okumura T, Ohtsuka T, Nakamura M. Primary recurrence in the lung is related to favorable prognosis in patients with pancreatic cancer and postoperative recurrence. World J Surg. 2017;41:2858–66.
62. Kim S, Itchins M, Arena J, Nahm C, Pavlakis N, Clarke S, et al. Patterns and determinants of recurrence for pancreatic ductal adenocarcinoma after resection. J Pancreas. 2017;18:458–64.
63. Groot VP, Daamen LA, Hagendoorn J, Borel Rinkes IHM, van Santvoort HC, Molenaar IQ. Use of imaging during symptomatic follow-up after resection of pancreatic ductal adenocarcinoma. J Surg Res. 2018;221:152–60.
64. Boone BA, Zeh HJ, Mock BK, Johnson PJ, Dvorchik I, Lee K, et al. Resection of isolated local and metastatic recurrence in periampullary adenocarcinoma. HPB (Oxford). 2014;16:197–203.
65. Groot VP, Wolfgang CL, He J. ASO author reflections: do distinct patterns of recurrence impact the prognosis of patients with resected pancreatic ductal adenocarcinoma? Ann Surg Oncol. 2018;25:806–7.
66. Wangjam T, Zhang Z, Zhou XC, Lyer L, Faisal F, Soares KC, et al. Resected pancreatic ductal adenocarcinomas with recurrence limited in lung have a significantly better prognosis than those with other recurrence patterns. Oncotarget. 2015;6:36903–10.
67. Latil A, Bieche I, Chene L, Laurendeau I, Berthon P, Cussenot O, et al. Gene expression profiling in clinically localized prostate cancer: a four-gene expression model predicts clinical behavior. Clin Cancer Res. 2003;9:5477–85.
68. Lapointe J, Li C, Higgins JP, van de Rijn M, Bair E, Montgomery K, et al. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. Proc Natl Acad Sci U S A. 2004;101:811–6.
69. Takeno A, Takemasa I, Seno S, Yamasaki M, Motoori M, Miyata H, et al. Gene expression profile prospectively predicts peritoneal relapse after curative surgery of gastric cancer. Ann Surg Oncol. 2010;17:1033–42.
70. Groot VP, Daamen LA, Hagendoorn J, Borel Rinkes IH, Busch OR, van Santvoort HC, et al. Current strategies for detection and treatment of recurrence of pancreatic ductal adenocarcinoma after resection: a nationwide survey. Pancreas. 2017;46:e73–5.
71. Daamen LA, Groot VP, Intven MP, Besselink MG, Busch OR, Groot Koerkamp B, et al. Postoperative surveillance of pancreatic cancer patients. Eur J Surg Oncol. 2019;45:1770–7.
72. Groot VP, van Santvoort HC, Rombouts SJE, Hagendoorn J, Borel Rinkes IH, van Vulpen M, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. HPB (Oxford). 2017;19:83–92.
73. Ryan JF, Groot VP, Rosati LM, Hacker-Prietz A, Narang AK, McNutt TR, et al. Stereotactic body radiation therapy for isolated local recurrence after surgical resection of pancreatic ductal adenocarcinoma appears to be safe and effective. Ann Surg Oncol. 2018;25:280–9.
74. Kim YI, Song KB, Lee YJ, Park KM, Hwang DW, Lee JH, et al. Management of isolated recurrence after surgery for pancreatic adenocarcinoma. Br J Surg. 2019;106:898–909.

Chapter 75
Patient-Reported Outcomes and Quality of Life in Pancreatic Cancer

Lisa M. Wintner, Monika Sztankay, and Bernhard Holzner

Take Home Messages

- Patient-reported outcomes are the gold standard to assess patients' quality of life using validated questionnaires.
- Before choosing a quality of life questionnaire, the purpose, timing and required content must be considered.
- Modern assessment software is able to collect, process, calculate and present quality of life electronically in real time. Especially the increased data quality and the possibility of easy and cost-effective remote assessments (outside of the hospital setting) are major strengths of this assessment method.
- Linking quality of life data to cut-off scores and thresholds enables indicating scores with clinically relevant impairments or changes and guiding which issues require further discussion and clinical action.

Pearls and Pitfalls

- Patients are the experts for reporting their quality of life. They provide valuable information, which can inform their health care and disease management.
- Validated instruments allow for the standardized assessment of quality of life of pancreatic cancer patients, considering their specific symptom burden (e.g. measuring pancreatic pain, gastrointestinal symptoms, weight loss, and taste changes).

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- Electronic assessment of patient's quality of life data bears many advantages, (as immediate data processing, more complete data, automatically generated reports) and eye-catching cross-sectional or longitudinal quality of life data profiles ease its incorporation into the medical consultation.
- There is still a need to catch up with promoting the use of quality of life data for shared-decision making and daily clinical routine.
- Successful implementation of patient-reported outcome assessments into clinical routine remains a challenge, as it requires the alignment of multiple interacting stakeholders on different levels of the clinical system.

Future Perspectives

- To encourage stakeholders to engage in routine quality of life assessments, recommendations for strategic and standardized implementation procedures should be developed and disseminated.
- Evidence-based and scientifically sound learning material needs to be developed to inform and educate health care professionals. A profound understanding of quality of life data and how it can be used in routine care will promote its actual use.
- The development of standardized assessment procedures and care pathways would support the uptake of routine quality of life assessments in daily clinical care, e.g. which measures are encouraged being used at different stages of pancreatic cancer including respective treatment recommendations.
- Real-world data is needed to identify the impact of quality of life assessments and quality of life data use on the allocation of resources and the use of health care services.

75.1 Introduction

Pancreatic cancer is a lethal disease with an almost one-to-one ratio of new cases (ranked 13th) and cancer deaths (ranked 7th) worldwide in 2018 [1]. As it is commonly diagnosed at an advanced stage, the rate for 5-year-survival is only about 9% across all tumour stages with a more favourable outcome for resectable localized disease [2]. As 80–85% of patients are not eligible for surgery at the time of diagnosis [3], their prognosis is mostly poor and they have to deal with debilitating symptoms caused by the disease itself and/or the aggressive multimodal treatment. Hence, the patient's quality of life (QOL) is paramount to both determining treatment goals and evaluating treatment success.

75.2 Patient-Reported Outcomes and Quality of Life

Discussing the patients' subjective view of their health status has always been an important part in modern clinical care, as a variety of symptoms and issues are only accessible for clinicians through patients' self-reports. Only the respective person

him- or herself can tell if and in which intensity certain symptoms occur (e.g. pain, depression, fatigue), if he or she feels impaired in his or her social life or if e.g. sleeping disturbances have been a problem. Such information can be summarised under the umbrella term Patient-Reported Outcomes (PROs) and includes all statements made by patients about their own health status and the possible effects of treatment they receive. More importantly, PROs are assessed without any interpretation, evaluation or modification by third parties [4]. Those self-reports of patients can encompass a variety of aspects like, amongst others, functioning (e.g. physically, socially, emotionally), symptoms (e.g. anxiety, nausea, vomiting, hair loss), satisfaction with care, perceived value of care or adherence to treatment regimen. QOL is a multidimensional construct that includes aspects of a patient's perspective of his/ her health status and can be best captured by the PRO methodology (Fig. 75.1). Most QOL questionnaires capture physical, psychological (anxiety, depression) and social aspects, query symptoms (e.g. pain, sleep disorders, impairment due to weight gain/loss) and ideally also topics that are of particular relevance to the respective patient group (e.g. for pancreatic cancer patients: altered peristalsis and taste changes after pancreatic surgery, abdominal pain, anorexia or weight loss).

75.3 Standardized Assessment of Quality of Life

It is already common practice to discuss the patient's symptoms and subjective health status during the medical encounter, but the duration, depth and focus of this discussion largely depends on the clinician and his/her knowledge and personal interest in QOL. The documentation is unspecific and inevitably contains both a selection and an interpretation by the health care professional. It may even happen that a detailed conversation about symptoms and impairments has taken place, but that it is not noted or traceable in the medical records. Furthermore, other factors can impact whether and in what way QOL is part of the medical encounter (e.g. stressful days with many patients, many difficult cases, few staff due to absences, etc. hinder to dedicate time to QOL issues) (Box 75.1).

Usually, questionnaires are used to assess the patient's QOL. Patients are required to complete these measures as independently as possible to obtain their unaltered perspective. It is also possible to conduct the questionnaires as interviews or to have them assessed by relatives, although these methods require special caution (specially trained staff, specific instruction of relatives). As such proxy ratings are likely to involve to some extent an interpretation process similar to that of clinicians' ratings, preference should be given to independent completion of questionnaires by the patients themselves.

Choosing a QOL assessment instrument requires the careful evaluation of its methodological and content-related quality, which is why the purpose of the assessment should be clear in advance. Questionnaires differ in their suitability for e.g. a general QOL screening, the evaluation of QOL during or after a certain treatment or for QOL follow-up. Attention must also be paid to the timing of data collection and the recall period of the used PRO measure, as before a medical intervention other areas might be relevant than shortly after or in long-term follow-up [5] and symptoms might occur with a delay, e.g. after administration of chemotherapy [6].

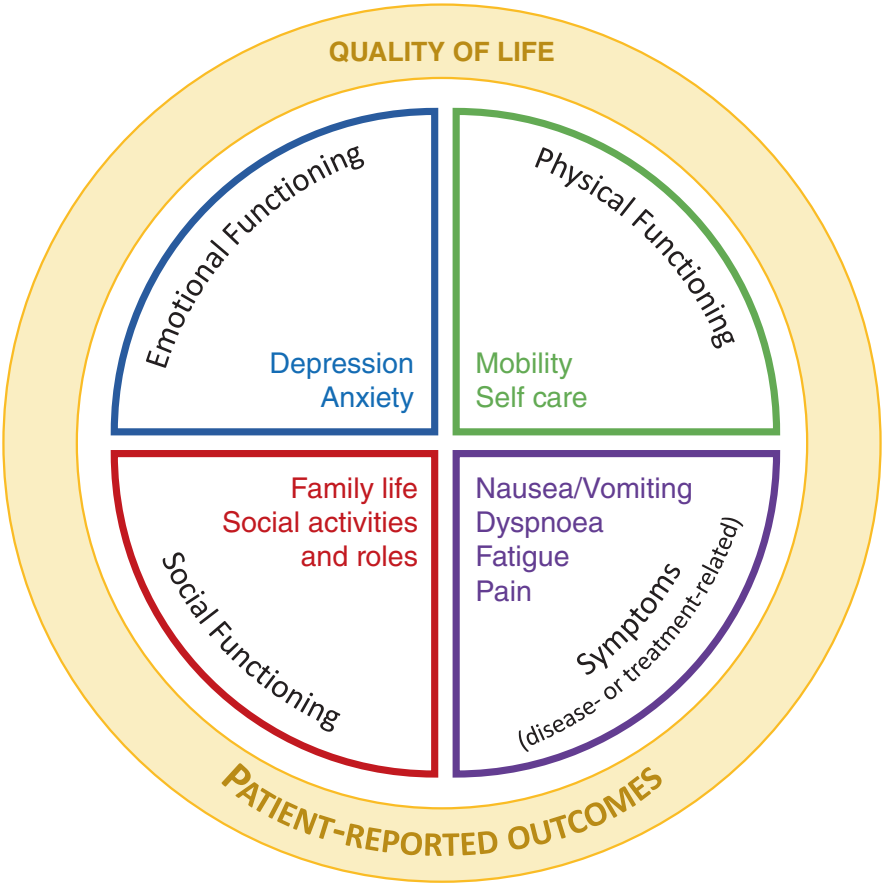

Fig. 75.1 schematically depicts the characteristics of PROs and QOL and their theoretical association. However, not all patient statements can be assigned to the concept of PROs. If patients share their impressions on how they experienced the delivery of health care (e.g. waiting times, access to services, involvement in decision-making or timing of assistance), this is referred to as "patient-reported experiences" (PREs). Those are commonly used as an indicator for quality of care and patient-centeredness of services. Regardless of their conceptual differences, the gold standard for the assessment of PROs and PREs is the use of validated questionnaires

Box 75.1 PRO Measures—Not Just the Reinvention of the Wheel

- **PRO measures** provide a reliable method of **complementing established outcome parameters** with a standardized assessment of the patient's perspective in order to gain a comprehensive and integrated picture of the patient's health status.
- By implementing PROs and the resulting standardized assessment of patients' QOL, the so far common practice of informally discussing QOL

during medical appointments is raised to a **higher level of professionalization**.

- Integrating **QOL data documentation** into the electronic medical record **ensures its accessibility** to clinicians and other health care professionals, increases its transparency and allows to follow the development of symptoms across a longitudinal trajectory.
- As time is more and more becoming one of the most precious resources in a busy clinical workflow, **QOL data can add to a more effective allocation of resources**, especially if it is used in conjunction with thresholds and cut-off scores indicating clinically relevant changes in QOL. Highlighted scores can guide the medical encounter and **help** the clinician **to focus on those aspects that require further immediate attention** due to clinical relevance.
- **QOL data** is not only of interest for clinical routine, but **also contributes to scientific knowledge** (gained from real world data as well as from clinical study data), can complement clinical registries and can be used for quality assurance, benchmarking and health technology assessment analyses.

75.4 Quality of Life Measures for Pancreatic Cancer Patients

There is broad range of QOL assessment instruments available. Besides generic measures, which can be used irrespective of a person's health status or a patient's diagnostic group, there are also questionnaires available, which take special account of the needs of a certain disease group (e.g. oncological patients). A recent review, dedicated to the identification of PRO measures in pancreatic cancer patients, provides a broad overview of instruments used in this population group including those targeting QOL [7].

The choice of a generic or specific questionnaire should consider how the data collected will be used. For comparisons with a norm sample of the general population, generic instruments are useful, although disease-relevant areas are often neglected and their sensitivity to changes is low [8, 9]. In order to document the individual QOL trajectory of patients and to evaluate treatment decisions regarding their effect on QOL, disease- and/or treatment-specific measures should preferably be used. If several QOL measures are combined to capture a broader picture of the patient's perspective, it is important to strike a careful balance between the quantity of items and their content. Merely focusing on the length of QOL measures could lead to neglecting QOL issues that are actually important for patients. Therefore, questionnaires should be chosen in such a way that they complement each other meaningfully with as few repetitions as possible [10]. Table 75.1 provides an overview of the most common generic and oncology specific QOL questionnaires or questionnaire systems including their instruments targeting pancreatic cancer.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ), the Functional Assessment of Chronical Illness Therapy (FACIT) and the Patient-Reported Outcomes Measurement Information System (PROMIS) are measurement systems for QOL in cancer

Table 75.1 Generic and disease-specific QOL instruments

Generic QOL-instruments		QOL-instruments in oncology	
WHOQOL	World Health Organization Quality Of Life Assessment Instrument [11]	EORTC-QLQ system	European Organisation of Research and Treatment of Cancer [12] QLQ-C30 Core questionnaire (30 items), diagnostic specific modules *EORTC QLQ-PAN26 (26 items)* [13]
EQ-5D	Euro Quality of Life—5 Dimensions) [14]	FACIT system	Functional Assessment of Chronic Illness Therapy [15] FACT-G Core questionnaire (27 items), diagnostic specific modules *FACT-Hep: FACT-G and the Hepatobiliary Subscale (HS, 18 items)* [16]
SF-36	Short-Form Health Survey 36 [17]	PROMIS-CANCER	Patient-Reported Outcomes Measurement Information System [18] *Eight gastrointestinal domains are available but none specific for pancreatic cancer*
SIP	Sickness Impact Profile [19]	MDASI-GI	M.D. Anderson Symptom Inventory [20] MDASI: 19 item symptom severity and interference with function inventory *MDASI-GI: includes five additional GI-specific symptom items*

patients with a modular structure. This means that a core questionnaire can be supplemented with diagnosis-specific modules or symptom indices. Furthermore, single items can be used to complement those "static" questionnaires, if important symptoms or issues are missing. As an example, the EORTC Item Library includes all items, scales and questionnaires that have been developed by the EORTC Quality of Life Group (QLG, https://qol.eortc.org) and a search function enables to quickly navigate through available measures. Since the EORTC QLQ-C30 and its disease specific module for malignancies of the pancreas QLQ-PAN26 and the FACT-Hep are the two most commonly used PRO measures to assess QOL in pancreatic cancer patients [7], those measures are described in more detail below.

75.4.1 Disease Specific Measures for Pancreatic Cancer

The **EORTC QLQ-PAN26** targets QOL in pancreatic cancer patients and its 26 items cover the domains Pancreatic Pain, Digestive, Altered bowel habit, Hepatic, Body image, Health care satisfaction, and Sexuality. It is used as a disease-specific module for the EORTC QLQ-C30, a generic questionnaire originally developed for

EORTC QLQ-PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4

Fig. 75.2 Specimen of the first five questions of the EORTC QLQ-PAN26 (© EORTC)

the assessment of cancer patients' QOL in clinical trials. Except for the Physical Functioning scale of the QLQ-C30, the questionnaires use a recall period of 1 week and all items are rated on a 4-point Likert-scale ("not at all", "a little", "quite a bit", "very much", see Fig. 75.2). The validation of the QLQ-PAN26 in a mixed sample of pancreatic cancer patients is still pending, but there is a report on the psychometric characteristics of the questionnaire in pancreas-resected patients [21]. A recent study investigated the content validity of the QLQ-PAN26, stating that it is conceptually relevant, though it might further benefit from adding items regarding neuropathic symptoms [22]. Though the QLQ-C30 is available in more than 100 languages, translations of the QLQ-PAN26 so far only cover the ten European languages, which have been used for questionnaire development [13]. Regarding the interpretation of QOL scores assessed with EORTC measures, reference values [23], minimal important differences [24–26], clinically relevant thresholds for the QLQ-C30 and the QLQ CAT measures [27, 28] and general population normative data [29] are available.

The **FACT-Hep** comprises 45 items and is a combination of the fourth version of the FACT-G and a Hepatobiliary Subscale. The FACT-G has initially been developed and validated in cancer patients with mixed diagnoses and different disease stages and consists of 27-items covering four QOL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. The disease-specific hepatobiliary cancer subscale combines questions being relevant for patients with hepatobiliary cancers (liver, bile duct and pancreatic cancer) including back and stomach pain, anorexia, gastrointestinal symptoms, weight loss and jaundice. All items use a recall period of 1 week and a 5-point Likert-scale ("not at all", "a little bit", "somewhat", "quite a bit", and "very much", see Fig. 75.3). The FACT-Hep is available in 43 languages. There are recommendations for the interpretation of raw score changes, but only for the FACT-G [30].

FACT-Hep (Version 4)

Please circle or mark the number per line to indicate your response as it applies to the past 7 days.

ADDITIONAL CONCERNS		Not at All	A Little	Some-what	Quite a Bit	Very Much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4

Fig. 75.3 Specimen of the first five questions of the Additional Concerns of the FACT-Hep (© FACIT)

75.5 Challenges of Routine QOL Assessments

There is a fundamental discrepancy between acknowledging the importance of patient's QOL and its integration into daily clinical care: While figures on mortality, morbidity, laboratory values and complication rates are established methods for evaluating treatments and disease progression, routine QOL assessments have not yet been fully implemented in clinical routine and do not represent a standard outcome measure. Many clinicians lack familiarity with the concept of QOL as well as specific knowledge on how to handle systematically collected QOL data. A common concern is that routine QOL assessments will additionally burden existing resources without offering clinical benefit [31]. There is still a widespread opinion that a patient's QOL can be sufficiently rated by a clinician, though it is well researched that the concordance between clinician's ratings and patient's self-reports is often poor and even decreases over time [32–37]. Though the importance of PROs is broadly acknowledged, there are attempts to reduce the concept of QOL to the assessment of disease symptoms, physical functioning and adverse events [38]. Other criticisms are problems regarding the comparability of different PRO measures and doubts about the methodology of QOL assessment, as patients are supposed to not being able to make "true" statements about their condition and recall biases might influence the scores [39]. In the context of the current development towards a more participatory approach in medical care, it is important to acknowledge that QOL data represents a structured record of the patients' subjective experience of specific areas of their health. These parameters are important in order to determine whether the patient's QOL has been positively influenced by medical interventions and recommendations regarding routine QOL assessments are increasingly being incorporated into evidence-based guidelines for oncological treatment [40–42].

75.6 Benefits of Routine QOL Assessments

Routine assessment of patient's QOL helps to improve communication with their health care professionals (e.g. increased discussion of symptoms [43, 44]). Patients themselves benefit from the use of PRO instruments, if clinicians explicitly use their collected QOL data [44]. Incorporating QOL data in their medical encounter helps clinicians to develop a better understanding of the patient's functional level and subjective health status [45], to bring up intimate and otherwise often overlooked issues [45, 46], and to discuss chronic non-specific symptoms (e.g., sleep disorders, fatigue, loss of appetite) [44] without increasing the consultation time. In addition, the routine collection of QOL enables the identification of areas requiring treatment and the prompt referral of patients [47], which promotes patient-centred and individually tailored treatment [48, 49] and improves symptom management. Patients whose practitioners had access to QOL information reported better continuity of care than patients who did not complete QOL instruments at all. They also felt that treatment choices have been made with more consideration for their daily activities, emotional well-being and QOL [50]. Participatory decision-making can result in patients having greater confidence in their treatment decision, being more satisfied with the therapy, having a higher feeling of self-efficacy and greater trust in their caregivers [51]. QOL data even has predictive value for traditional clinical outcomes such as survival (Box 75.2) [24, 52, 53].

Box 75.2 Positive Effects of Using PRO Data in Clinical Care

- improved communication
- better understanding of the patients' functional level and subjective health status
- facilitated discussion of intimate or overlooked issues
- more frequent discussion of chronic non-specific symptoms
- no prolonging effect on consultation time
- identification of need for clinical intervention and referral
- facilitation of patient-centred care and individually tailored treatment
- improved symptom management
- better continuity of care
- participatory decision-making empowers patients and increases their trust in their care
- QOL has predictive value for survival

In addition to complex constructs such as QOL, PROs can also provide information about the patient's view of the occurrence and intensity of treatment toxicities. The Common Toxicity Criteria of Adverse Events (CTCAE) of the National Cancer Institute have been further developed into a PRO instrument (PRO-CTCAE) [54] for

those domains, which can be assessed by patients themselves. Using this new measure, ratings of adverse events, which underestimate in particular the occurrence of mild toxicities [55], can be meaningfully supplemented by the patient perspective [56]. However, neither PRO-CTCAE nor other symptom indices are an adequate substitute for established QOL instruments that are superior in terms of content validity [56]. A content analysis of the PRO-CTCAE and the EORTC QLQ instruments reports similar results since the EORTC QLQ system covers considerably more areas relevant to oncological surgery and radiotherapy than PRO-CTCAE [57].

75.7 Use of Electronic Data Collection Methods in Clinical Routine

Assessing QOL electronically solves many hurdles imposed by conventional paper-pencil questionnaire data collection. Because patients enter their data directly, there are no transmission errors or data loss due to lost sheets of paper. Preparing a questionnaire is less laborious, might even be carried out automatically and the application of multilingual instruments increases inclusiveness. Furthermore, collecting data electronically benefits from immediate storage, data processing and automated score calculation, making the data immediately available to health care personnel right after the questionnaire has been completed. Normative data, thresholds and cut-off scores allow identifying and highlighting clinically relevant impairments. In this way, QOL data can be used for structuring and guiding the medical encounter by focusing on areas of special interest and in need of further in-depth discussion. In particular, the use of interfaces (e.g. using common Health Level 7 standards) simplifies the exchange of data between hospital information systems and electronic PRO systems and supports the automation of administrative processes. Next to a smooth integration of QOL data assessment into the existing clinical workflow, easy access to PRO data is an important aspect to promote their use by medical staff [58]. Electronic data assessment is necessary for the use of computer-adaptive testing (CAT), which achieves greater measurement precision with a smaller number of questions and thus reduces the burden on patients. In addition, the patients are given items relevant to them, as the questions to be asked are selected based on the previously given answers.

There is a broad range of assessment software available, most of which offer a variety of functionalities like data collection, processing and storage, score calculation and generation of cross-sectional or longitudinal reports, study monitoring and remote data collection including patient portals [59]. The Computer-based Health Evaluation System [60] (www.ches.pro, Fig. 75.4) is an example of a software solution which, due to its modular approach, can be used for QOL assessments in clinical routine, for conducting clinical studies and for clinical registries alike. Most software systems are internet-based, which means that access to the system is location independent. This is especially important for the use of patient portals with individual login data for patients. They facilitate to collect QOL data cost-effectively before, during, in between

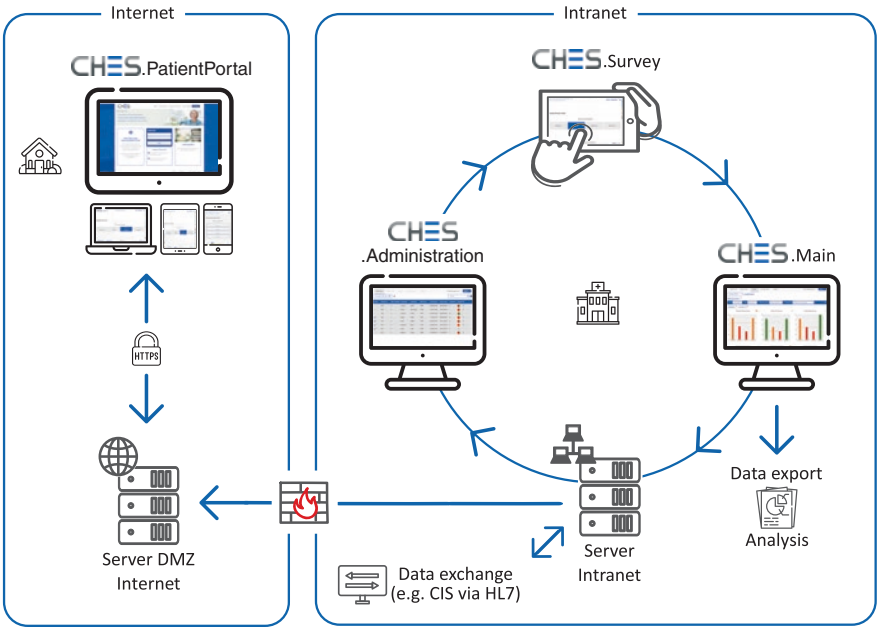

Fig. 75.4 Functionalities and structure of the Computer-based Health Evaluation System (CHES [60]) as an example for an electronic system assessing QOL

and after hospital stays as follow up. In addition to data assessment, such portals can also have other functionalities, such as providing trustworthy information on the disease and treatment, a presentation of one's own QOL data with tailored self-management recommendations, and information on available health care services and their contact details. In a cohort of pancreatic and periampullary cancer undergoing pancreaticoduodenectomy, an App regularly collecting QOL data, providing tailored self-care advice and triggering alerts to a dedicated nurse who took immediate clinical action showed to be beneficial in terms of symptom control. Although the QOL scores of the patient group using the App and the control group were similar after 6 months, those of the App group indicated more stable QOL over time and especially better scores 6 weeks after surgery. They reported higher emotional functioning, fewer digestive symptoms and less pancreatic pain, less worry about low weight, less nausea/vomiting, less appetite loss, less pain, and less constipation than the control group [61].

75.8 Conclusion

Patients are the experts for their subjective health status and validated QOL questionnaires can make their experience accessible to health care professionals in a structured way. Integrating PRO data in clinical care enhances the patient-clinician

communication and promotes participatory decision-making, individual treatment management and the evaluation of medical interventions. Electronic QOL assessment contributes to effective data collection and processing, facilitates the collection of PROs outside the hospital setting (e.g. QOL data entry at home before hospital visits or long-term follow-up via a patient portal), provides additional information to patients and facilitates the use of QOL data for the medical encounter (e.g. immediate availability, application of thresholds, identification of clinically relevant symptoms and impairments). Hence, the collection of longitudinal data provides a detailed insight into the course of the disease and its treatment.

Acknowledgments Icons used within Fig. 75.4 made by Freepik from www.flaticon.com.

Conflicts of interest: Bernhard Holzner holds intellectual property rights of the CHES software. The other authors do not state any conflict of interest.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–53.
2. National Cancer Institute. SEER cancer stat facts: pancreatic cancer. Bethesda, MDSeer 18 2009–2015. https://seer.cancer.gov/statfacts/html/pancreas.html.
3. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846–61.
4. U.S. Department of Health and Human Services. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.
5. Neville A, Lee L, Antonescu I, Mayo NE, Vassiliou MC, Fried GM, et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. Br J Surg. 2014;101(3):159–70.
6. Giesinger JM, Wintner LM, Zabernigg A, Gamper EM, Oberguggenberger AS, Sztankay MJ, et al. Assessing quality of life on the day of chemotherapy administration underestimates patients' true symptom burden. BMC Cancer. 2014;14:758.
7. Maharaj AD, Samoborec S, Evans SM, Zalcberg J, Neale RE, Goldstein D, et al. Patient-reported outcome measures (PROMs) in pancreatic cancer: a systematic review. HPB (Oxford). 2019;22(2):187–203.
8. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
9. Rautalin M, Färkkilä N, Sintonen H, Saarto T, Taari K, Jahkola T, et al. Health-related quality of life in different states of breast cancer – comparing different instruments. Acta Oncol. 2018;57(5):622–8.
10. Rolstad S, Adler J, Rydén A. Response burden and questionnaire length: is shorter better? A review and meta-analysis. Value Health. 2011;14(8):1101–8.
11. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46(12):1569–85.
12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.

13. Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer. 1999;35(6):939–41.
14. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337–43.
15. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes. 2003;1:79.
16. Cella D, Butt Z, Kindler HL, Fuchs CS, Bray S, Barlev A, et al. Validity of the FACT Hepatobiliary (FACT-Hep) questionnaire for assessing disease-related symptoms and health-related quality of life in patients with metastatic pancreatic cancer. Qual Life Res. 2013;22(5):1105–12.
17. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305(6846):160–4.
18. Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH roadmap cooperative group during its first two years. Med Care. 2007;45(5 Suppl 1):S3–S11.
19. Gilson BS, Gilson JS, Bergner M, Bobbit RA, Kressel S, Pollard WE, et al. The sickness impact profile. Development of an outcome measure of health care. Am J Public Health. 1975;65(12):1304–10.
20. Wang XS, Williams LA, Eng C, Mendoza TR, Shah NA, Kirkendoll KJ, et al. Validation and application of a module of the M. D. Anderson Symptom Inventory for measuring multiple symptoms in patients with gastrointestinal cancer (the MDASI-GI). Cancer. 2010;116(8):2053–63.
21. Eaton AA, Karanicolas P, MChir C, Allen P, Gonen M. Psychometric validation of the EORTC QLQ-PAN26 pancreatic cancer module for assessing health related quality of life after pancreatic resection. J Pancreas. 2017;18:19–25.
22. Herman JM, Kitchen H, Degboe A, Aldhouse NVJ, Trigg A, Hodgin M, et al. Exploring the patient experience of locally advanced or metastatic pancreatic cancer to inform patient-reported outcomes assessment. Qual Life Res. 2019;28(11):2929–39.
23. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30 reference values manual. Belgium: EORTC; 2008.
24. Musoro ZJ, Hamel JF, Ediebah DE, Cocks K, King MT, Groenvold M, et al. Establishing anchor-based minimally important differences (MID) with the EORTC quality-of-life measures: a meta-analysis protocol. BMJ Open. 2018;8(1):e019117.
25. Musoro JZ, Coens C, Fiteni F, Pogoda K, Cardoso F, Russell NS, et al. Minimally important differences for interpreting EORTC QLQ-C30 Scores in Patients with advanced breast cancer jnci cancer spectrum. JNCI Cancer Spectr. 2019;3(3)
26. Cocks K, King MT, Velikova G, de Castro G Jr, Martyn St-James M, Fayers PM, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713–21.
27. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol. 2020;118:1–8.
28. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, et al. Thresholds for clinical importance were defined for the European Organisation for Research and Treatment of Cancer Computer Adaptive Testing Core-an adaptive measure of core quality of life domains in oncology clinical practice and research. J Clin Epidemiol. 2020;117:117–25.
29. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based

on 15,386 persons across 13 European countries, Canada and the United States. Eur J Cancer. 2019;107:153–63.
30. Cella D, Hahn EA, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between improvement and worsening. Qual Life Res. 2002;11(3):207–21.
31. Locklear T, Miriovsky BJ, Willig JH, Staman K, Bhavsar N, Weinfurt K, et al. Strategies for overcoming barriers to the implementation of patient-reported outcomes measures. An NIH Health Care Systems Research Collaboratory Patient Reported Outcomes Core White Paper. https://sites.duke.edu/rethinkingclinicaltrials/tools-for-research/strategies-for-overcoming-barriers-to-the-implementation-of-patient-reported-outcomes-measures/. 2014. Accessed 22 Oct 2019.
32. Atkinson TM, Rogak LJ, Heon N, Ryan SJ, Shaw M, Stark LP, et al. Exploring differences in adverse symptom event grading thresholds between clinicians and patients in the clinical trial setting. J Cancer Res Clin Oncol. 2017;143(4):735–43.
33. Chidambaram S, DeShields T, Potter P, Olsen S, Chen L. Patient and provider concordance on symptoms during the oncology outpatient clinic visit. J Community Support Oncol. 2014;12(10):370–7.
34. Barata A, Martino R, Gich I, García-Cadenas I, Abella E, Barba P, et al. Do patients and physicians agree when they assess quality of life? Biol Blood Marrow Transplant. 2017;23(6):1005–10.
35. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care. 2008;14(8):530–9.
36. Wilson KA, Dowling AJ, Abdolell M, Tannock IF. Perception of quality of life by patients, partners and treating physicians. Qual Life Res. 2000;9(9):1041–52.
37. Stephens RJ, Hopwood P, Girling DJ, Machin D. Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Qual Life Res. 1997;6(3):225–36.
38. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Am Soc Clin Oncol Educ Book. 2016;35:67–73.
39. Bossola M, Murri R, Onder G, Turriziani A, Fantoni M, Padua L. Physicians' knowledge of health-related quality of life and perception of its importance in daily clinical practice. Health Qual Life Outcomes. 2010;8:43.
40. Association of Comprehensive Cancer Centres (ACCC). Oncoline Cancer Clinical Practice Guidelines. 2018. http://www.oncoline.nl/index.php. Zugriff am 01 Aug 2018.
41. Deutsche Krebsgesellschaft (DKG). Leitlinienprogramm Onkologie. 2018. https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft/leitlinien.html. Zugriff am 01 Aug 2018.
42. DH on behalf of the National Health Service in England. Guidance on the routine collection of Patient Reported Outcome Measures (PROMs). 2008. http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_092625.pdf. Zugriff am 01 Aug 2018.
43. Takeuchi EE, Keding A, Awad N, Hofmann U, Campbell LJ, Selby PJ, et al. Impact of patient-reported outcomes in oncology: a longitudinal analysis of patient-physician communication. J Clin Oncol. 2011;29(21):2910–7.
44. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol. 2004;22(4):714–24.
45. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA. 2002;288(23):3027–34.
46. Taenzer P, Bultz BD, Carlson LE, Speca M, DeGagne T, Olson K, et al. Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients. Psychooncology. 2000;9(3):203–13.

47. Smith SK, Rowe K, Abernethy AP. Use of an electronic patient-reported outcome measurement system to improve distress management in oncology. Palliat Support Care. 2014;12(1):69–73.
48. Duman-Lubberding S, van Uden-Kraan CF, Jansen F, Witte BI, van der Velden LA, Lacko M, et al. Feasibility of an eHealth application "OncoKompas" to improve personalized survivorship cancer care. Support Care Cancer. 2015;24(5):2163–71.
49. Warrington L, Absolom K, Velikova G. Integrated care pathways for cancer survivors – a role for patient-reported outcome measures and health informatics. Acta Oncol. 2015;54(5):600–8.
50. Velikova G, Keding A, Harley C, Cocks K, Booth L, Smith AB, et al. Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: secondary outcomes of a randomised controlled trial. Eur J Cancer. 2010;46(13):2381–8.
51. Kane HL, Halpern MT, Squiers LB, Treiman KA, McCormack LA. Implementing and evaluating shared decision making in oncology practice. CA Cancer J Clin. 2014;64(6):377–88.
52. Denis F, Lethrosne C, Pourel N, Molinier O, Pointreau Y, Domont J, et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. J Natl Cancer Inst. 2017;109(9)
53. Rees JR, Rees M, McNair AG, Odondi L, Metcalfe C, John T, et al. The prognostic value of patient-reported outcome data in patients with colorectal hepatic metastases who underwent surgery. Clin Colorectal Cancer. 2016;15(1):74–81.e1.
54. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106(9)
55. Falchook AD, Green R, Knowles ME, Amdur RJ, Mendenhall W, Hayes DN, et al. Comparison of patient- and practitioner-reported toxic effects associated with chemoradiotherapy for head and neck cancer. JAMA Otolaryngol Head Neck Surg. 2016;142(6):517–23.
56. Groenvold M, Aaronson NK, Darlington AE, Fitzsimmons D, Greimel E, Holzner B, et al. Focusing on core patient-reported outcomes in cancer clinical trials-letter. Clin Cancer Res. 2016;22(22):5617.
57. O'Connell Francischetto E, Gilbert A, Velikova G, Blazeby J. Is the CTCAE system suitable to use in trials in surgery and radiotherapy? A content analysis of the NCI-PRO-CTCAE and EORTC systems. In: Quality of life research, vol. 23. Amsterdam: Elsevier; 2014.
58. Fritz F, Dugas M. Are physicians interested in the quality of life of their patients? Usage of EHR-integrated patient reported outcomes data. Stud Health Technol Inform. 2013;192:1039.
59. Jensen RE, Snyder CF, Abernethy AP, Basch E, Potosky AL, Roberts AC, et al. Review of electronic patient-reported outcomes systems used in cancer clinical care. J Oncol Pract. 2014;10(4):e215–22.
60. Holzner B, Giesinger JM, Pinggera J, Zugal S, Schopf F, Oberguggenberger AS, et al. The Computer-based Health Evaluation Software (CHES): a software for electronic patient-reported outcome monitoring. BMC Med Inform Decis Mak. 2012;12:126.
61. Gustavell T, Sundberg K, Segersvärd R, Wengström Y, Langius-Eklöf A. Decreased symptom burden following surgery due to support from an interactive app for symptom management for patients with pancreatic and periampullary cancer. Acta Oncol. 2019;58(9):1307–14.

Part X
Palliation and End of Life Issues

Chapter 76
Palliative Care in Pancreatic Cancer

Hartwig Kørner, Geoffrey Dunn, and Jon Arne Søreide

In 1942, George O. Whipple, who pioneered the only curative procedure for pancreatic ductal carcinoma, wrote in a review of his eponymous operation: "the considerable risk (i.e., operative mortality) of 30–35% is justified if they (the patients) can be made comfortable for a year or two" [1]. Decades later, the worthiness of efficacious palliation for patients with this diagnosis suggested in his statement remains unchanged. Unfortunately, the grim survival statistics for patients with pancreatic ductal carcinoma have also not significantly changed. Despite this, much progress has been made in making cancer patients and their families "comfortable for a year or two" with the increasing familiarity and availability of evidence-based palliative care.

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Take Home Messages

- Palliative care aims to improve and secure optimal quality of life for patients with incurable disease
- Palliative care is guided by individual treatment goals and the patient's expectations for the remaining lifetime
- Careful symptom assessment, preferable by validated tools, is the key for effective palliative care
- End-of-life care intends to preserve the dignity of the patient and the family during the last weeks of life in cooperation with the palliative team
- Surgeons are important part of the palliative team

Future Perspectives

- Future studies on palliative surgical care should focus on patient-reported outcomes in terms of validated tools for symptom assessment and quality of life rather than survival
- Studies addressing palliative surgical care should have a prospective design and include a randomized design whenever possible
- The distinction between *palliative treatment* (patient-centered approach) and *non-curative treatment* (disease-centered approach) is crucial to improve the knowledge base of palliative surgical care

76.1 Introduction

The present chapter on palliative care for patients with pancreatic cancer intends to provide the basic knowledge for surgeons to recognize patients who need palliative care, to assess the symptom burden of their disease, and to secure the benefit of possible interventions for symptom control by careful considerations guided by the individual preferences for the remaining life time. As life-threatening disease involves all aspects of life, the palliative team approach has been established to meet the needs of the patient and their families, and the surgeon should be part of the team [2, 3].

As a highly lethal malignancy, pancreatic ductal adenocarcinoma (PDAC) is among the fourth and sixth leading causes of cancer-related death in the USA and Europe [4, 5], and in contrast to a number of other malignant tumors (e.g. kidney, bladder, endometrium, breast, ovary, colorectum, melanoma) the index-cancer deaths of pancreas cancer has remained stable over years [6]. The incidence has increased slightly, both in females and males, with an overall mortality almost similar to the incidence. However, during the last decade the survival has improved, with a 5-year relative survival between 9–9.7% [4]. However, as reported by Cooperman and coworkers [5], the estimated 5-year survival rates mostly between 1–3% are observed in population-based studies from Australia, China, USA, and the Scandinavian countries.

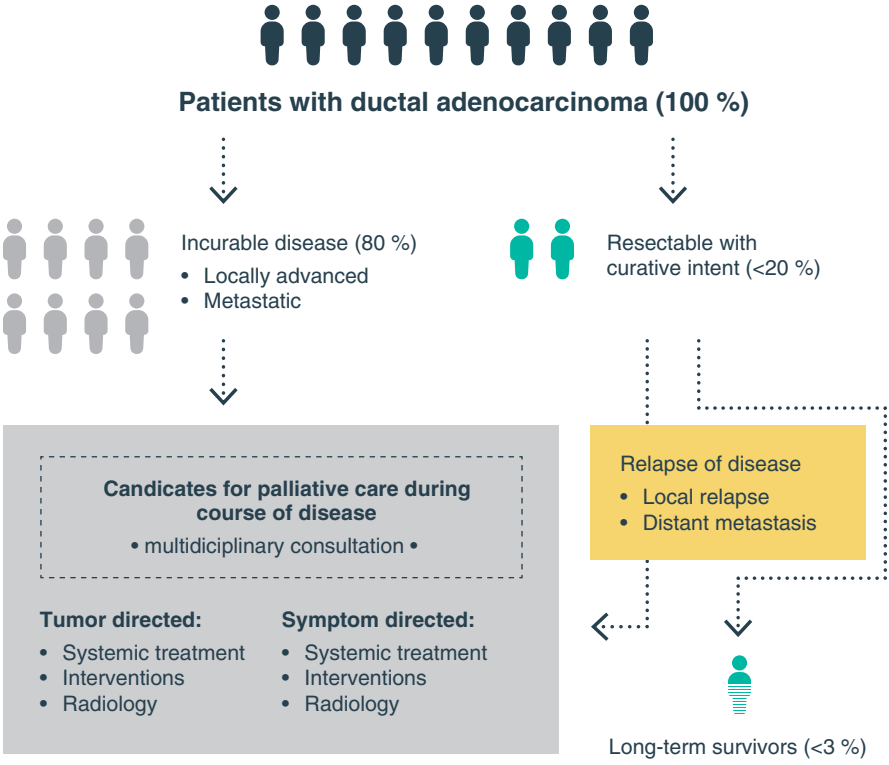

Fig. 76.1 Distribution of patients in an unselected cohort with pancreatic ductal adenocarcinoma with regard to stage of disease at diagnosis and treatment options

Most patients (80–85%) present with either local advanced disease or distant metastases [7] (Fig. 76.1). In addition, some patients are not regarded as surgical candidates, due to serious comorbidity, higher age, general frailty or based on the patient's individual decision. Accordingly, only a small proportion (≈15–20%) of the pancreatic cancer patients are eligible for surgical therapy with curative intent. Even after pancreaticoduodenectomy, the prognosis is in general poor, with early relapse of disease in many patients and a 5-year survival of ≈25–30%, and even worse (10%) in node-positive patients [4, 7, 8].

Obviously, in a large proportion of patients diagnosed with PDAC the need for and timing of palliative care should be contemplated.

76.2 The Concept of Palliative Cancer Care

The concept of palliative care is not an innovation but a rediscovery of what had once been the core moral principle of care for the sick: *comfort always*. Historically, the practice of medicine was mainly based on empiric knowledge with limited

prospects of cure. During the nineteenth century, the scientific and industrial paradigm shift changed medicine profoundly and was paralleled by increased focus on cure of diseases, in part because of the success in eradicating diseases. Numerous surgical procedures for current standard cancer treatment evolved during the late nineteenth and earlier twentieth century, such as gastric resection and the Miles' operation for rectal cancer. The success of these interventions contributed to the acceptance of the disease-centered approach that is the current paradigm of industrial medicine. The repercussions of this were insidious and profound as patients whose conditions did not yield to cure realized they were of less interest to the professionals caring for them than the luckier patients. Worse than unfortunate, they saw themselves as "failures".

The English nurse, social worker, and physician Dr. Cicely Saunders, driven by the sufferings of patients and friends who died of cancer, laid the foundation for current palliative care with her work pioneering modern hospice care during the 1960s. She is considered the most prominent protagonist of palliative care as a natural part of modern medicine [9]. Her concept of "total pain" which she described in the early 1960s has become the basis for palliative needs assessment [10]. Total pain is the summation of physical, psychological, socioeconomic, and spiritual or existential pain. The World Health Organization defines palliative care as "… *an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*." [11] (Table 76.1).

Presently, palliative care is considered an integral part of modern medicine and treatment of incurable diseases. In many countries, palliative medicine is established as a specialty or subspecialty.

Table 76.1 WHO definition of palliative care

Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:
• provides relief from pain and other distressing symptoms
• affirms life and regards dying as a normal process
• intends neither to hasten or postpone death
• integrates the psychological and spiritual aspects of patient care
• offers a support system to help patients live as actively as possible until death
• offers a support system to help the family cope during the patients illness and in their own bereavement
• uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
• will enhance quality of life, and may also positively influence the course of illness
• is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

Table 76.2 Statement of principles of palliative surgical care

1. Respect the dignity and autonomy of patients, patients' surrogates, and caregivers
2. Honor the right of the competent patient or surrogate to choose among treatments, including those that may or may not prolong life
3. Communicate effectively and empathically with patients, their families, and caregivers
4. Identify the primary goals of care from the patient's perspective and address how the surgeon's care can achieve the patient's objectives
5. Strive to alleviate pain and other burdensome physical and nonphysical symptoms
6. Recognize, assess, discuss, and offer access to services for psychological, social, and spiritual issues
7. Provide access to therapeutic support, encompassing the spectrum from life-prolonging treatments through hospice care, when they can realistically be expected to improve the quality of life as perceived by the patient
8. Recognize the physician's responsibility to discourage treatments that are unlikely to achieve the patient's goals, and encourage patients and families to consider hospice care when the prognosis for survival is likely to be less than a half-year
9. Arrange for continuity of care by the patient's primary and/or specialist physician, alleviating the sense of abandonment patients may feel when "curative" therapies are no longer useful
10. Maintain a collegial and supportive attitude toward others entrusted with care of the patient

The Task Force on Surgical Palliative Care of the American College of Surgeons and The ACoS Committee on Ethics issued *The Statement of Principles of Palliative Care* in 2005. This is considered the principal guideline for surgeons caring for patients with serious life-limiting, critical, and terminal illness [12] (Table 76.2). The statement is guidance for surgeons to look beyond our operative skills and focus on treatment goals as defined by the individual patient, based on an expanded view of the disease and its implications for the patient and those identified by the patient as family [2, 13]. Since 2012 The American College of Surgeons Commission on Cancer has required access to palliative care services in order to qualify for cancer program certification.

76.3 The Palliative Patient with Unresectable or Metastatic Pancreatic Cancer

Curative treatment will be beyond the scope of a realistic treatment goal for most patients with pancreatic cancer, including those with relapse after intended curative primary treatments. Depending on the subjective burden of disease, including clinical challenges like pain, obstructive jaundice, gastric outlet symptom, ascites and others, a number of therapeutic approaches should be considered to alleviate discomfort and ease troublesome symptoms (Fig. 76.2). Surgical, endoscopic and radiologic interventions are available to relieve obstructions. The technical aspects of these procedures are covered elsewhere in this textbook (see Chap. 76.8).

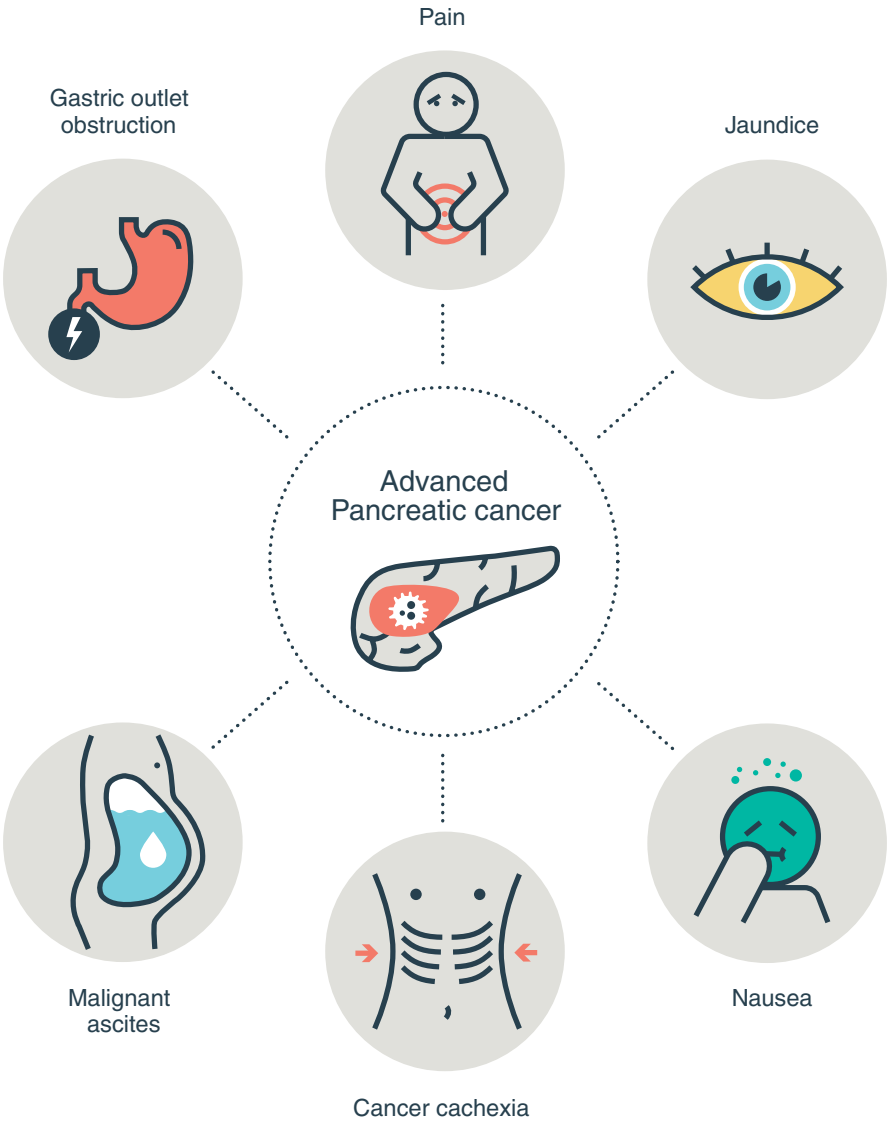

Fig. 76.2 The six most common symptoms in patients with incurable pancreatic cancer

Effective palliative care, including palliative interventions, to relieve symptoms is based on thorough assessment of the extent of the disease together with the patient's needs beyond the physical domain. In addition to local symptoms caused by the tumor, unintended weight loss and signs of reduced physiological reserves such as protein loss/cachexia and declined ability to exercise are telling clues. Beyond this, attention should be directed to daily life concerns, such as housing, family relations, emotional, and spiritual needs [14–16].

76.4 Approach to the Palliative Patient

Empathetic communication is the bridge to the palliative patient [17, 18]. The disclosure of the bad news of incurable disease associated with a dismal prognosis and significant morbidity is a trial for even the most positive physician-patient relationship. However, it also provides a unique opportunity to strengthen mutual confidence and trust. A trusting relationship between the doctor or other health care providers and the patient and the family forms the necessary platform for the ups and downs that will occur during the illness's trajectory. Trust is most reliably achieved by open and honest information about the details of investigations in context with genuine interest in the patient's perspectives on life. The conventional message driven by the disease-centered approach that "there is nothing more to be done" should be turned into the honest commitment to do everything that is meaningful to preserve quality of life and relieve symptoms. Good knowledge about the treatment options of modern palliative medicine and the assurance of non-abandonment are prerequisites to re-frame despair into realistic hope. For less experienced surgeons it is advised to include a more seasoned surgical colleague or experienced member of a palliative care team in these discussions.

The "Host-directed approach" or "patient-centered approach" identifies the disease-specific factors underlying physical complaints in the context of the patient's life (e.g. age, social status, family-related issues or existential concerns). This approach preserves patient autonomy, which means no decisions are made without the full participation of the individual patient and others the patient specifies. In modern medical practice, paternalization of patients by health care providers is no longer acceptable [19–21], and avoidance of non-beneficial treatment is a duty for those caring for patients with advanced pancreatic cancer [22, 23].

76.5 End-of-Life Care

End-of-life care aims to provide terminally ill patients and their families the necessary health care to alleviate physical and psychological symptoms and to solve social and spiritual problems. The amount and type of help is characterized by the unique situation of the individual patient. As a consequence, the definition of end-of-life care depends on medical, but also non-medical factors such as culture or religion [24]. The provision of satisfactory care during the final path of life towards death is highly complex and demands specialized palliative care provided by the palliative team and is beyond the scope of this chapter. However, it is a strong obligation for the clinician to identify the palliative patient with short remaining lifetime due to advanced disease and to provide access to specialist palliative care. Usually, the question "would you be surprised if this patient would be alive in x months" ("surprise question") is considered as a useful tool for clinicians to

estimate the expected remaining lifetime and the need for end-of-life care. Usually, expected lifetime of 6 months or less warrants to consider the need of end-of-life care. However, these considerations are difficult, and estimates differ strongly between clinicians and various health professions [25].

76.6 Assessment of the Palliative Patient

Appropriate symptom control requires a thorough assessment of the patient's symptom burden. This includes not only clinical impressions of function and abilities but also the use of symptom and functional scores.

76.7 Assessment of Function

The Karnofsky performance status [26] and the ECOG functional score [27] are the most commonly used functional scores. They have additionally been correlated with prognosis for lower scores in specific patient populations. While the Karnofsky score ranks function from 0 to 100, the ECOG score lists five subgroups from 0 (unlimited function) to 5 (death) (Table 76.3). The latter score is considered as the most practical scoring system in daily practice. More aggressive treatment, i.e. surgery and/or oncological treatment can be considered for ECOG status of 0–2, while ECOG status 3 or higher is regarded as a strong indicator to restrain treatment to symptom-directed conservative treatment options. Reduced physical function is related to *cancer cachexia syndrome*. The ability to induce a catabolic state with increased waste of protein and fat tissue refractory to nutritional measures is particularly characteristic of pancreatic cancer [28].

Table 76.3 Eastern Cooperative Oncology Group (ECOG) performance status[a]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house-work, office-work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a]Can also be calculated by use of the internet resources at: https://www.mdcalc.com/eastern-cooperative-oncology-group-ecog-performance-status

76.8 Assessment of Symptoms

Assessment of the patient's specific symptoms should include a broader and systematic screening of the most common symptoms (Fig. 76.2) experienced by patients with advanced pancreatic cancer or other malignancies, i.e. the revised Edmonton Symptom Assessment System (ESAS-r) [29] (Table 76.4). This score addresses the ten most frequent complaints reported by palliative patients, such as pain, pain evoked by movement, dyspnea, loss of appetite, insomnia, anxiety and depression, each of them assessed by a visual analog scale (VAS) between 0 (symptom not present) and 10 (unbearable). Usually, a score between 4 and 6 requires adjustment of treatment, a score of 7 or higher requires immediate action to secure acceptable symptom control. Serial measurement of the ESAS-r score over time will help to monitor the effect of treatment adjustment on symptoms experienced by the patient. The ESAS-r score is considered as the most essential tool for assessment of palliative patients and is considered basic knowledge for palliative care by physicians. The ESAS-r score should be part of referral to the palliative team and be available on outpatient clinics and wards with responsibility for patients with advanced cancer.

A number of perioperative factors have been evaluated with regard to estimate survival expectancy in patients with advanced pancreatic cancer [30, 31]. For patients with unresectable pancreatic cancer, Jamal et al. [32] reported four symptoms that independently predicted poor survival. These include weight loss >10%, pain, jaundice and smoking. Each symptom was weighted by the authors, from

Table 76.4 Edmonton Symptom Assessment System (revised version) (ESAS-r)

Please circle the number that best describes how you feel NOW:												
No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
No tiredness	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
(Tiredness = lack of energy)												
No drowsiness	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
(Drowsiness = feeling sleepy)												
No nausea	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
No lack of appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible lack of appetite
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
No depression	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
(Depression = feeling sad)												
No anxiety	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
(Anxiety = feeling nervous)												
Best well-being	0	1	2	3	4	5	6	7	8	9	10	Worst possible well-being
(Well-being = how you feel overall)												
No_____	0	1	2	3	4	5	6	7	8	9	10	Worst possible _____
Other problem (for example, constipation)												

Patient name: _____
Date: _____
Time: _____

Table 76.5 McGill-Brisbane Symptom Score (MBSS) for pancreatic cancer

Symptom	Points
Weight loss >10%	8
Pain	5
Jaundice	4
Smoking	4
Total possible	**21**

Low MBSS = 0–9 → median overall survival 14.6 months
High MBSS = 12–21 → median overall survival 6.3 months

which they developed the McGill-Brisbane Symptom Score (MBSS) (Table 76.5) which in their study showed a better predictive value than the presence or absence of distant metastasis [32]. While such a score, or any combination of various clinical factors, may represent a practical and ready-to-use tool, a validation of the score in different populations is of great importance before the true prognostic value of any score can be confirmed.

76.9 Assessment of Trajectory of Disease

In addition to functional status and symptom assessment, knowledge of where the patient stands in the disease trajectory (Fig. 76.3) is necessary to plan treatment. The trajectory typically includes tumor-directed treatment (a) until a decision to postpone treatment due to lack of effect has been made, at which point the patient often is observed (b) until the disease accelerates (c). During this time, palliative treatment options may be considered, and become more important when progressing disease is accompanied by increased suffering. Rapid deterioration indicates the need for end-of-life care (d), and any interventions are contraindicated.

The traditional view that palliative care starts when curative options are no longer available has recently been challenged by the concept of "early integration of palliative care into oncological treatment" [33–37]. This approach describes cancer care as a continuum from treatment aimed at cure to palliative care, rather than two tandem processes that exclude each other. However, more knowledge is needed to substantiate these findings, and currently there is no evidence with specific regard to pancreatic cancer.

76.10 Goals and Achievements for the Palliative Patient

The final goal of assessment of the palliative patient is to define the *individual treatment goal* [14, 38, 39]. This treatment goal is defined by what the patient may experience as the most severe complaints, but also the most important expectations and wishes for the remaining lifetime. The individual treatment goal will strongly vary between patients with comparable features of their cancer disease, depending on

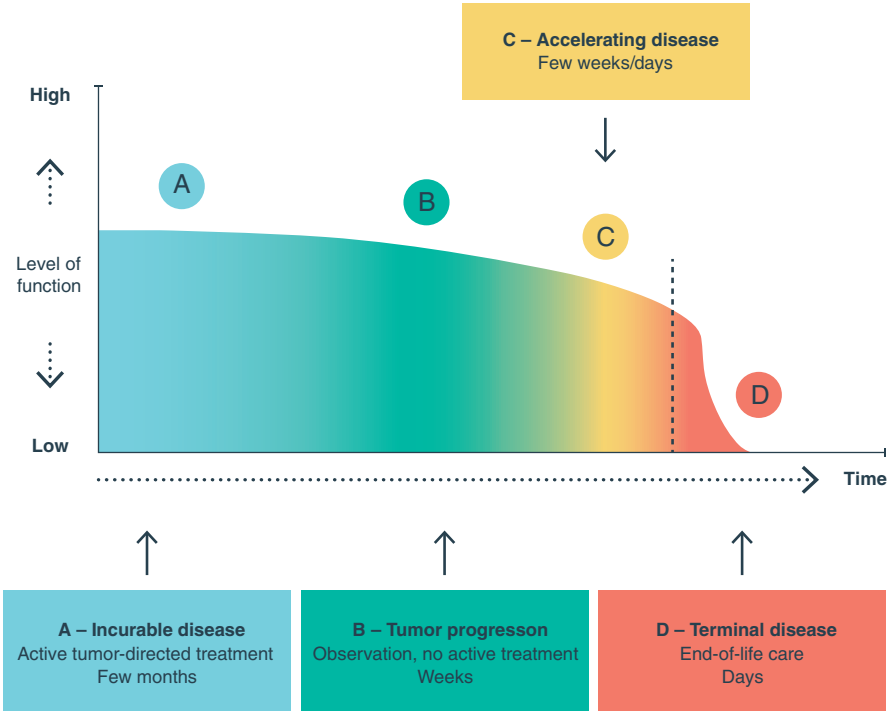

Fig. 76.3 Trajectory of incurable pancreatic cancer disease with regard to functional ability of the patient over time. Active tumor-directed treatment (**a**) followed by observation during progressive disease (**b**), accelerating disease (**c**) and rapid deterioration and need of end-of-life care (**d**)

age, function and their general view on life. Thus, any treatment option needs to be considered to which degree it is likely to help the patient to achieve his/her individual goal with a minimum of harm. The prognostic information obtained from the assessment of where the patient is in the disease trajectory is necessary to guide the patient and the family's decision about the level of invasiveness of treatment, i.e. choice between major surgical procedures and non-operative intervention, less risky intervention [14]. Failure to couple the patient's perspective with symptom assessment and patient understanding of prognosis risks reduced quality of life, major morbidity, even premature death.

76.11 Palliative Surgical Interventions

The primary aim of palliative surgical intervention (palliative surgery) is the relief of burdensome symptoms, though life prolongation could be considered a secondary goal [38].

No intervention whether major operative intervention or minor percutaneous procedures are excluded from consideration as long as the intervention results in

relief of burdensome symptoms identified by the patient and morbidity and mortality are acceptable. In contrast to most medical treatment, palliative surgery is irreversible and has the risk of surgical morbidity and mortality. Peri-operative risk is a major topic of shared decision-making when the indication for palliative surgical intervention is discussed. Because the aim of a palliative surgical procedure is symptom relief and improved quality of life, any adverse event would only amplify existing distress of the patient and the family without the benefit of improved survival. Because of this, palliative surgical interventions are strongly discouraged in asymptomatic patients or as a prophylactic measure [14, 36, 40].

No discussion of palliative surgery is complete without a joint understanding of the continued plan of care in the event of an adverse outcome, especially if it would require initiation of invasive life support and or other ICU care. *Advance directives,* which include *code status,* are meant to provide guidance for these contingencies. To protect patient autonomy and prevent future family anguish, it is highly recommended to review existing advance directives for clarification and amendment or drafting them prior to initiation of invasive treatment. The key to achieve patient satisfaction is the principle of patient-centered care [41]: to do what will serve the patient to reach the individual treatment goal does not necessarily mean "to do whatever is possible" [19].

76.12 Where Does the Surgeon Fit in?

76.12.1 Treatment Decisions

Treatment recommendations based on appropriate diagnostics and good knowledge of tumor biology are discussed at the MDT meeting and presented by the surgeon to the patient. This encounter offers the opportunity to review the recommendation in the light of the patient's physical needs, comorbidities and expectations. The surgeon is the key person to give advice to assure a beneficial outcome for the patient. Good knowledge of the range of curative and palliative treatment options and empathetic communication is the basis of optimal counselling. This is particularly true for patients suffering from a disease with a dismal prognosis such as pancreatic cancer.

76.12.2 Research on Surgical Palliative Care—Challenges and Opportunities

Research on surgical palliative care is scarce and hampered by unclear definitions of the term "palliative", which is mostly used as a synonym for "non-curative" without addressing the effect of treatments on symptom relief [19]. Moreover, most studies are retrospective cohort studies of heterogenous populations. Very few randomized controlled trials have been published [42, 43], and consequently, the evidence of palliative surgical interventions is of low quality and often limited to survival as outcome.

Scientific evaluation of palliative surgical care should focus on the effect of treatments on the patient's symptom burden. This can be done by adequate quality of life measurement tools, e.g. the EORTC QLQ PAN26 (https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-PAN26-English.pdf) combined with the general measurement tool EORTC QLQ C30 (https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf) for cancer diseases.

To measure and compare the effect on the individual treatment goal of palliative interventions raises methodological challenges. For this purpose, the Palliative Surgical Outcome Score (PSOS) was proposed in 2003 [44]. This score measures the time outside the hospital as compared to time in hospital related to palliative interventions, and a ratio of ≥70% of the time at home is considered as a proxy for satisfactory symptom control achieved by the procedure. The PSOS, which has recently been evaluated in patients undergoing palliative treatment of large bowel obstruction using self-expanding metal stents [45], is not specific for any cancer disease, and is suggested as a useful tool for evaluation of interventions to relieve symptoms caused by advanced pancreatic cancer.

76.12.3 Education in Palliative Treatment for Surgeons—Building a Culture

Surgeons have an obligation to identify the patient with palliative needs and refer to the palliative team when appropriate and available. They should regard themselves as an essential part of the extended palliative team. Over a continuum of surgical care, many surgeons have established a surgeon–patient relationship based on mutual trust and respect over time [46]. In light of this covenantal relationship for surgeons and patients in rural and urban locations, many complaints and symptoms should be solved by the knowledgeable and interested general surgeon [40, 47, 48]. This would increase the clinically relevant availability to palliative cancer care. Although the field of cancer surgery likely has recently benefited by innovative thinking and evidence-based knowledge, a recent survey demonstrated surgical oncology programs in the US provide insufficient education and assessment of palliative care [3].

76.13 Future Directions

Despite some progress, pancreatic cancer still challenges both sides of the patient/family–surgeon relationship. As Whipple pointed out long ago, the opportunity to relieve distress and promote function through palliation is the worthiest antidote for the distressing reality of uncommon cure [1]. Surgeons should not let the grail of cure distract them from the humanity of contributing uniquely and substantially to symptom relief. With the increased attention to quality of life outcomes by the public and health care professionals, it is axiomatic that an increased focus on palliative care in surgical education and research will be necessary for surgeons caring for patients through the entire spectrum of pancreatic cancer [3, 40, 47, 48].

76.14 Conclusion

Although the field of palliative care has been mostly developed by non-surgeons, surgeons have increasingly shown interest in it because of its appeal to the core moral principle of surgery—non-abandonment. Palliative care challenges some of our most basic assumptions about the meaning of illness prompting us to ask new questions and discover new problems. As surgeons, we have a long tradition of service in the relief of suffering that precedes our recent accomplishments in curative treatment. We can restore that tradition without compromising cure as we endorse an approach to care that equally values the relief of suffering and the elimination of disease.

References

1. Whipple AO. Present-day surgery of the pancreas. N Engl J Med. 1942;226:515–26.
2. Rialon K. Integration of palliative surgery into the Palliative Care Delivery Team. J Palliat Care Med. 2013;02(02) https://doi.org/10.4172/2165-7386.1000e115.
3. Larrieux G, Wachi BI, Miura JT, Turaga KK, Christians KK, Gamblin TC, et al. Palliative care training in surgical oncology and hepatobiliary fellowships: a national survey of program directors. Ann Surg Oncol. 2015;22(Suppl 3):S1181–6.
4. Cancer in Norway 2017—Cancer incidence, mortality, survival and prevalence. Oslo Cancer Registry of Norway; 2018.
5. Cooperman AM, Bruckner H, Snady H, Hammerman H, Fader A, Feld M, et al. Cancer of the pancreas-actual 5, 10, and 20+ year survival: the lucky and fortunate few. Surg Clin North Am. 2018;98(1):73–85.
6. Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, et al. Causes of death among cancer patients. Ann Oncol. 2017;28(2):400–7.
7. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016;388(10039):73–85.
8. Pokrzywa CJ, Abbott DE, Matkowskyj KA, Ronnekleiv-Kelly SM, Winslow ER, Weber SM, et al. Natural history and treatment trends in pancreatic cancer subtypes. J Gastrointest Surg. 2019;23(4):768–78.
9. Puchalski CM, Sbrana A, Ferrell B, Jafari N, King S, Balboni T, et al. Interprofessional spiritual care in oncology: a literature review. ESMO Open. 2019;4(1):e000465.
10. Saunders C, Sykes N. The management of terminal malignant disease. 3rd ed. London: Edward Arnold; 1993.
11. WHO. WHO definition of palliative care. https://www.who.int/cancer/palliative/definition/en/.
12. Task Force on Surgical Palliative C, Committee on E. Statement of principles of palliative care. Bull Am Coll Surg. 2005;90(8):34–5.
13. Miller P. The time is always right to do what is right for our patients. Surg Clin North Am. 2019;99(5):xix–xxiii.
14. Cook MR. Goals of care: understanding the outcomes that matter most. Surg Clin North Am. 2019;99(5):833–47.
15. Søreide JA. Palliative surgical care. Br J Surg. 2010;97(7):970–1.
16. Fogel EL, Shahda S, Sandrasegaran K, DeWitt J, Easler JJ, Agarwal DM, et al. A multidisciplinary approach to pancreas cancer in 2016: a review. Am J Gastroenterol. 2017;112(4):537–54.
17. Sommovilla J, Kopecky KE, Campbell T. Discussing prognosis and shared decision-making. Surg Clin North Am. 2019;99(5):849–58.
18. Whitelaw S, Clark D. Palliative care and public health: an asymmetrical relationship? Palliat Care. 2019;12:1178224218819745.
19. Hofmann B, Håheim LL, Søreide JA. Ethics of palliative surgery in patients with cancer. Br J Surg. 2005;92(7):802–9.

20. Lo B, Ruston D, Kates LW, Arnold RM, Cohen CB, Faber-Langendoen K, et al. Discussing religious and spiritual issues at the end of life: a practical guide for physicians. JAMA. 2002;287(6):749–54.
21. Miner TJ, Jaques DP, Tavaf-Motamen H, Shriver CD. Decision making on surgical palliation based on patient outcome data. Am J Surg. 1999;177(2):150–4.
22. Willmott L, White B, Gallois C, Parker M, Graves N, Winch S, et al. Reasons doctors provide futile treatment at the end of life: a qualitative study. J Med Ethics. 2016;42(8):496–503.
23. Alesi E, Bobb B, Smith TJ. Guiding patients facing decisions about "futile" chemotherapy. J Support Oncol. 2011;9(5):184–7.
24. Gysels M, Evans N, Menaca A, Higginson IJ, Harding R, Pool R, et al. Diversity in defining end of life care: an obstacle or the way forward? PLoS One. 2013;8(7):e68002.
25. White N, Kupeli N, Vickerstaff V, Stone P. How accurate is the 'Surprise Question' at identifying patients at the end of life? A systematic review and meta-analysis. BMC Med. 2017;15(1):139.
26. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984;2(3):187–93.
27. Kobayashi S, Ueno M, Kameda R, Moriya S, Irie K, Goda Y, et al. Duodenal stenting followed by systemic chemotherapy for patients with pancreatic cancer and gastric outlet obstruction. Pancreatology. 2016;16(6):1085–91.
28. Porporato PE. Understanding cachexia as a cancer metabolism syndrome. Oncogenesis. 2016;5:e200.
29. Watanabe SM, Nekolaichuk CL, Beaumont C. The Edmonton Symptom Assessment System, a proposed tool for distress screening in cancer patients: development and refinement. Psychooncology. 2012;21(9):977–85.
30. Ouyang H, Ma W, Liu F, Yue Z, Fang M, Quan M, et al. Factors influencing survival of patients with pancreatic adenocarcinoma and synchronous liver metastases receiving palliative care. Pancreatology. 2017;17(5):773–81.
31. Gray PJ Jr, Wang J, Pawlik TM, Edil BH, Schulick R, Hruban RH, et al. Factors influencing survival in patients undergoing palliative bypass for pancreatic adenocarcinoma. J Surg Oncol. 2012;106(1):66–71.
32. Jamal MH, Doi SA, Simoneau E, Abou Khalil J, Hassanain M, Chaudhury P, et al. Unresectable pancreatic adenocarcinoma: do we know who survives? HPB (Oxford). 2010;12(8):561–6.
33. Kaasa S, Loge JH. Early integration of palliative care-new evidence and old questions. Lancet Oncol. 2018;19(3):280–1.
34. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet. 2014;383(9930):1721–30.
35. Schlick CJR, Bentrem DJ. Timing of palliative care: when to call for a palliative care consult. J Surg Oncol. 2019;120(1):30–4.
36. Papanicolas I, Figueroa JF. Preventable harm: getting the measure right. BMJ. 2019;366:l4611.
37. Vanbutsele G, Pardon K, Van Belle S, Surmont V, De Laat M, Colman R, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. Lancet Oncol. 2018;19(3):394–404.
38. Rhee C, McHugh M, Tun S, Gerhart J, O'Mahony S. Advantages and challenges of an interdisciplinary palliative care team approach to surgical care. Surg Clin North Am. 2019;99(5).
39. Cooperman AM. A symposium on pancreatic cancer: time for a paradigm shift. An overview and personal reflections. Surg Clin North Am. 2018;98(1):xvii–xx.
40. Dunn GP. Surgery, palliative care, and the American College of Surgeons. Ann Palliat Med. 2015;4(1):5–9.
41. Kupfer JM, Bond EU. Patient satisfaction and patient-centered care: necessary but not equal. JAMA. 2012;308(2):139–40.
42. Leblanc A, Legare F, Labrecque M, Godin G, Thivierge R, Laurier C, et al. Feasibility of a randomised trial of a continuing medical education program in shared decision-making on the

use of antibiotics for acute respiratory infections in primary care: the DECISION+ pilot trial. Implement Sci. 2011;6:5.
43. Staats PS, Hekmat H, Sauter P, Lillemoe K. The effects of alcohol celiac plexus block, pain, and mood on longevity in patients with unresectable pancreatic cancer: a double-blind, randomized, placebo-controlled study. Pain Med. 2001;2(1):28–34.
44. McCahill LE, Smith DD, Borneman T, Juarez G, Cullinane C, Chu DZ, et al. A prospective evaluation of palliative outcomes for surgery of advanced malignancies. Ann Surg Oncol. 2003;10(6):654–63.
45. Søreide JA, Tholfsen T, Karlsen LN, Kvaløy JT, Kørner H. Palliative surgical outcome score (PSOS) in patients treated palliatively with self-expanding metal stent (SEMS) for malignant incurable colorectal obstruction. Surg Oncol. 2019;29:134–9.
46. Toevs CC. Transitioning to comfort-focused care at the end of life. Surg Clin North Am. 2019;99(5):1019–27.
47. Bonanno AM, Kiraly LN, Siegel TR, Brasel KJ, Cook MR. Surgical palliative care training in general surgery residency: an educational needs assessment. Am J Surg. 2019;217(5):928–31.
48. Ballou JH, Brasel KJ. Surgical palliative care education. Surg Clin North Am. 2019;99(5):1037–49.

Chapter 77
Pain in Pancreatic Cancer: Mechanisms and Management

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Take Home Messages

- Pancreatic cancer pain sensation is of neuropathic origin. It is a complex process that is linked to neuro-cancer and neuro-immune interactions.
- The interlinked phenomena of neuroplasticity, neural remodeling, neural invasion and pancreatic neuritis are key factors of this phenomenon.
- The treatment of pancreatic cancer pain should consider its neuropathic and complex nature and should be carried out in a multidisciplinary fashion.

Pearls and Pitfalls

- Pharmacotherapy in pain management must follow a stepwise escalation of medications with increasing analgesic effect and including neuro-pharmaceuticals.
- In refractory cases interventional therapies may be applied. EUS guided neurolysis is considered effective and safe and may be advisable early in the course of refractory cases.
- Surgery for palliative pain management should only be used if all other options fail.

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Future Perspectives

- Research focusing on the treatment of neuropathic changes in pancreatic cancer may provide both a solution for the neuropathic pain sensations and improvement of the course of the disease via by controlling neural invasion.
- A novel treatment regime with anti-neurotrophic agents together with standard chemotherapeutics should be tested whether this regime can better control local recurrence and with this the prognosis of the patients.

77.1 Introduction

Pain among pancreatic cancer is often described as a deep-delving abdominal pain penetrating to the back [1]. In the early stage of pancreatic cancer, only 30% of patients experience abdominal or back pain, while in limited disease this rate is 60% and in advanced pancreatic cancer 80% [1]. Since the disease is often diagnosed at advanced stage, up to 73% of patients complain of abdominal pain at diagnosis [1]. Aside from interfering with the quality of life [2], and being a disabling symptom, pain is a major predictor of survival in pancreatic cancer [3, 4]. Patients with resectable pancreatic cancer with no pain are reported to have a median survival time between 22–29 months, whereas this time is 15–19 months in patients with mild pain, and between 9–10 months in patients with moderate to severe pain [4, 5]. For this reason, pain is reported as a potential indicator of local recurrence and survival after pancreaticoduodenectomy [6]. The novel mechanisms suggested for the genesis of pancreatic pain, not only have translational relevance to treatment of pain, but also impact the course of pancreatic cancer.

Until recently, the mechanism of abdominal pain in pancreatic cancer was mainly attributed simply to mechanical pressure and/or the invasion of adjacent organs and the neural plexus by cancer cells [1, 7]. However, in the last two decades, thanks to advances in neuro-gastroenterology, we have a much more sophisticated understanding of the formation of pain in pancreatic cancer which includes alterations in the peripheral and central nervous system in reaction to the complex interaction between cancer cells, inflammatory cells, neurons and glial cells via neuro-humoral mediators, chemokines and their receptors [8, 9]. These neuropathic changes that influence and induce pain in pancreatic cancer comprise neural inflammation, neural invasion, neural plasticity and neural remodeling which are interlinked processes and correlate to the severity of neuropathic pain in pancreatic cancer [4, 9]. This chapter will be a summary of the present data regarding this complex mechanism and the suggested treatment for pancreatic cancer pain.

77.2 Mechanism of Pain

In the last decade, neuroplasticity has been the target of research in an effort to explain the mechanism in pancreatic cancer. Plasticity is a term that indicates the capability to reshape and react in a system in response to physical stimuli [9]. Neural

plasticity refers to the adaptive-reactive modifications of the peripheral and central nervous systems in reaction to stimuli which can also be associated with chronic diseases [9]. This phenomenon is increasingly recognized as a common feature of gastrointestinal (GI) nervous system during pathological states that has the potential to suppress, augment or even induce pathogenic events during GI disorders [9, 10].

77.3 Pancreatic Neuroplasticity and Neuropathic Pain

Neural plasticity in pancreatic cancer and chronic pancreatitis involves neuronal activation at the peripheral, spinal and supraspinal level [9]. At the periphery, in both of these inflammatory disorders of the exocrine pancreas, intrapancreatic nerves are remarkably enlarged and increased in number [4, 9]. This neural hypertrophy and increased neural density were reported to be even more apparent in pancreatic cancer when compared to chronic pancreatitis [4]. Increased neural density as well as neural hypertrophy are strongly associated with the degree of neural invasion in pancreatic cancer patients [4]. These findings are notable in regard to pain formation, since it was shown that in pancreatic cancer patients with severe abdominal pain, neural hypertrophy was much more evident. In addition, the patients whose nerves display endoneural invasion have higher frequency and intensity of pain when compared to the patients whose nerves only exhibit perineural invasion which is a milder form of neural invasion [4]. It is now accepted that neural invasion in pancreatic cancer and pancreatic neuroplasticity are closely associated [4]. The predominant alteration regarding nerves is intra and extra-pancreatic neural invasion by cancer cells [4, 11, 12]. In nearly all cases of pancreatic cancer, neural invasion can be demonstrated. Histopathological evaluation of pancreatic cancer shows distinctly increased number and size of intrapancreatic nerves. The examination of these hypertrophic nerves demonstrates a high frequency of neural invasion [8]. In a study, increased number and size of nerves were observed both in pancreatic tumor tissues and normal pancreatic tissues near pancreatic cancer, although neural hypertrophy was more apparent in cancer areas [13]. These neuroplastic changes were found to be associated with increased expression of neural plasticity marker, growth associated protein-43 (GAP-43) which was higher in normal pancreatic tissues near to tumor when compared to normal pancreatic tissues, and highest in pancreatic cancer tissues [13]. The presence of GAP-43 - whose expression is normally upregulated in neurons as a response to neuronal injury - in non-tumoral areas in patients with pancreatic cancer suggested that pancreatic cancer stimulated neuropathic changes around itself in a paracrine fashion. Also, it was demonstrated that Artemin and nerve growth factor (NGF) were overexpressed in pancreatic cancer tissues and tissues near pancreatic cancer [13]. Under physiologic conditions these two mediators stimulate neural proliferation and differentiation and favor neural outgrowth and sprouting [14–17]. However, expressed both by pancreatic cancer cells and intrapancreatic nerves [13, 18, 19], they also are known to act as chemo-attractants that enhance pancreatic cancer cell proliferation and invasion [13, 18, 19]. Thus, a vicious cycle is suggested in which neurotrophic factors such as NGF and Artemin

stimulate the pancreatic nerves to undergo neuroplastic changes and to transform into a richer source of NGF and Artemin attracting more pancreatic cancer cells. This should result in further NI in previously normal pancreatic tissue and extrapancreatic neural plexus [13]. These processes are closely related to pain, because in addition to its aforementioned effects, NGF is recognized as a mediator of pain. Its exogenous administration leads to hyperalgesia in animals, and significantly increases sensitivity to painful stimuli in humans [20]. NGF and its high-affinity receptor TrkA are markedly elevated in pancreatic cancer and have been associated with pain. On the contrary, artemin was not correlated with pain in pancreatic cancer, although it was correlated with the intensity and frequency of pain in chronic pancreatitis [20].

Capsaicin receptor, or transient receptor potential vanilloid type I (TRPVI) is another receptor that interacts with NGF and is overexpressed in pancreatic cancer [20]. TRPVI immunoreactivity was found in pancreatic cancer cells and nerves, especially the nerves infiltrated by pancreatic cancer cells and the ones in the inflamed tissue around the cancer [21]. It is expressed in neurons that are assumed to be nociceptors in which it is usually co-expressed with substance P and (calcitonin gene-related peptide) CGRP. It also colocalizes with TrkA. When TRPVI is activated, the release of substance P and CGRP from nerve terminals is stimulated, and the expression of TRPVI was found to be correlated with the severity of pain [20]. It also has a potential to be a therapeutic target since its agonist resiniferatoxin was demonstrated to induce apoptosis and inhibited pancreatic cancer cell growth [21]. Another mediator that seems closely linked to the pathophysiology of and the pain in pancreatic cancer is Fractalkine. The expression of its selective receptor CX3CR1 was detected in pancreatic cancer cells, though not in normal pancreatic ducts [22]. In the study by Marchesi et al. [23], it was demonstrated that CX3CR1(+) pancreatic cancer cell lines migrated in response to human recombinant fractalkine and they also specifically adhered to cells of neural origin expressing fractalkine [23]. These findings presented evidence that fractalkine and its receptor played an important role in NI in pancreatic cancer. Except mediating neural invasion, fractalkine also was previously shown in experimental neuropathic pain models to be released from dorsal root ganglia and was accompanied by upregulation of CX3CR1 in the spinal microglia with subsequent neuropathic pain behavior [22].

Similarly neurturin (NRTN) and its receptor glial-cell-derived neurotrophic factor receptor alpha-2 (GFRalpha-2) were studied for their role in pancreatic cancer pathophysiology and neuropathic pain [24]. It was demonstrated that a member of the glial-derived neurotrophic factor (GDNF) family, NRTN and its receptor GFRalpha-2 had an upregulation in nerves, pancreatic cancer cells and extracellular matrix in pancreatic cancer. The cancer tissues and Pancreatic cancer cells contained increased amounts of NRTN. This neurotrophic factor, for which pancreatic cancer cells seemed like a major source, lead to sustained proliferation and increased invasiveness. Moreover, it contributed to neuroplastic alterations, and interestingly, its suppression by hypoxia lead to enhanced targeted invasion of nerves. Considering that GFRalpha-2 was associated with severe abdominal pain sensation in pancreatic

cancer patients [24] NRTN/ GFRalpha-2 axis may be counted as one of many complex interactions in the mechanism of pain generation in pancreatic cancer.

77.4 Pancreatic Neuritis

Although not a hallmark of pancreatic cancer as neural invasion, perineural inflammation is a substantial contributor of visceral neuropathy and pain in pancreatic cancer [4, 25]. Indeed, in the study by Ceyhan et al. [4], the presence of pancreatic neural inflammation (neuritis) was found to be even more prominent in pancreatic cancer when compared to chronic pancreatitis patients. The investigators found that pancreatic cancer patients with severe pancreatic neuritis demonstrated a distinct increase in neural density, exhibiting the close link between neuroplasticity and pancreatic neuritis. In addition, the presence of pancreatic neuritis correlated with the severity of abdominal pain sensation [4]. This inflammatory process in pancreatic neuritis is suggested to be the pancreatic counterpart of the visceral neural inflammation present at other GI disorders such as inflammatory bowel disease, irritable bowel syndrome, and appendicitis, in which neuro-inflammation is associated with generation of pain and organ dysfunction [25, 26]. Neural inflammatory infiltration was further characterized in another study, which demonstrated that the dominant cell populations in pancreatic neuritis were cytotoxic T lymphocytes, macrophages and mast cells [25]. However, neuropathic pain in pancreatic cancer was only associated with increased mast cell infiltration around intrapancreatic nerves [25]. These cells are known to exhibit close association with peptidergic nerve fibers that contain substance P, calcitonin-gene-related-peptide or NGF that activate mast cells and induce their degranulation [25]. In return, this degranulation releases histamine, serotonin, NGF, and mast cell tryptase that also activate and sensitize neurons via their receptors resulting in pain and neuronal dysfunction [27].

77.5 Neural Remodeling

In addition to aforementioned neuropathic changes, neural remodeling which is a qualitative alteration in neural structure seems to contribute to neuropathic pain in pancreatic cancer. Namely, the nerves in pancreatic cancer patients contain much fewer sympathetic fibers when compared to normal pancreatic tissues. Moreover, increasing neural size and severity of neural invasion correlate with decreased amount of sympathetic nerve fibers [28]. These phenomena obtain relevance considering that sympathetic nervous system and especially noradrenaline has a complicated role in modulation of pain [29] and emphasizing the data that the suppression of sympathetic nerve fibers was found to be more obvious among patients who reported increased pain severity in pancreatic cancer [28].

As a summary, depending on the existing data, it can be speculated that neural damage initiated either by neural invasion or neural inflammation in pancreatic cancer stimulates neuropathic alterations via a number of neurotrophic and chemotactic factors, many of which themselves have nociceptive properties, further switching the neurochemical code toward preferential expression of neuropeptides such as substance P and CGRP that are frequently present in nociceptive neurons. The pain may even be further exaggerated by the invasion of adjacent celiac plexus by cancer cells [1].

77.6 Pain Management

Due to its complex mechanism and multiple causes, pain in pancreatic cancer is difficult to treat and requires multimodal management that includes noninvasive and invasive interventions by various disciplines. When planning this multidisciplinary management, severity, quality, distress and functional consequences of pain should be taken into account as well as the reasons of pain [3].

In the management of pain, first of all, secondary reasons should be excluded. If there are any, secondary reasons of pain often need specific treatments which are often effective [3]. Anastomotic and peptic ulcers are quite common and should be diagnosed with gastroscopy and be treated with proton pump inhibitors with or without the addition of *H. pylori* eradication therapy. Side effects of chemotherapy and irradiation such as neuropathy and enteritis may also result in pain and should be managed with local treatment and drugs against neuropathy [3]. Opioid use in this patient group also has its side effects including constipation, abdominal pain, and opioid induced hyperalgesia. In this case medication must be tapered and constipation should be attempted to be treated with laxatives if present [3]. In the cases with constipation refractory to conventional laxative therapy, methylnaltrexone is reported to be a safe and effective treatment, although its rarely reported side-effect, perforation, should be kept in mind in patients with peritoneal carcinomatosis [30]. After pancreatic resection, exocrine function insufficiency, bile acid malabsorption or bacterial overgrowth may be observed [3]. Pancreatic enzyme replacement therapy was shown to significantly improve abdominal pain, malabsorption, bloating, steatorrhea, diarrhea and quality of life [31]. A deficiency in bile acid absorption may be overcome with the administration of cholestyramine and bacterial overgrowth may be treated by antibiotics [3]. Complications of surgical or endoscopic procedures such as anastomotic leaks, strictures, intraabdominal adhesions or pancreatitis should be diagnosed by clinical evaluation and imaging and be addressed by conservative, endoscopic or surgical treatment [3]. Obstructive jaundice develops in 80% of patients with unresectable pancreatic head malignancies and gastric outlet or duodenal obstruction develops in approximately 10–25% of pancreatic cancer patients in the natural course of the disease [32]. Therefore, double by-pass procedure including the biliary-digestive and gastro-jejunal anastomosis was historically the standard treatment in unresectable pancreatic cancer [32]. However,

development of endoscopic stenting has changed this trend [32]. Basically, endoscopic stenting of gastric outlet obstruction is associated with shorter length of stay, and quicker resumption of oral intake, while surgery is associated with lower reintervention rates [32]. A recent Cochrane review recommended palliative surgery for patients with prolonged survival [33]. Currently, in patients with unresectable pancreatic cancer endoscopic biliary stenting is accepted as the gold standard for the treatment of obstructive jaundice. If this is unsuccessful or technically not feasible palliative biliary drainage can be performed percutaneously either via an internal metal stent or external drainage. Palliative surgery, nevertheless, still has a place if these two therapies are contraindicated or not feasible or in the case of recurrent obstruction of the stent in patients with good functional status and long life expectancy [32]. Also in patients with obstructed biliary duct and unresectable disease found at the time of surgery, biliary digestive anastomosis is still considered the best option in the case of good functional status and good expected prognosis [32]. Finally, pancreatic cancer may directly invade adjacent organs or form metastases to distant locations including bone, liver and lung which need multidisciplinary treatment according to the location [3].

For analgesic treatment, currently pharmacotherapy for pain in pancreatic cancer is still guided by the WHO analgesic ladder [3, 34, 35]. This concept represents a stepwise escalation of medications with increasing analgesic effect until pain relief is provided [35]. The administration of analgesics should preferably be orally and at regular intervals, and severe attacks of pain may be treated with fast-acting on demand opioids [3].

First step analgesic therapy must start with non-opioid painkillers such as acetaminophen and if need be, non-steroidal anti-inflammatory drugs (NSAID) with the combination of proton pump inhibitors [3, 34]. Metamizole is reported to be safer than NSAIDs for upper intestinal tract and kidneys and can also be used in the first-line treatment [3]. In the case of more severe pain, combination therapies, including opioids and adjuvant analgesics may be used to increase the effectiveness of the therapy and to decrease the side effects of the individual drugs [3, 36]. Adjuvant analgesics are a heterogenous group of drugs, including antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-noradrenalin reuptake inhibitors), anticonvulsants and anxiolytics [3]. Among these pregabalin, an anticonvulsant, has been effectively used to treat various pain disorders, including diabetic neuropathy [37], neuropathic pain of central origin [38] and most importantly pain in chronic pancreatitis [39] which shares neuropathic pathways with pain in pancreatic cancer. Its therapeutic gain in pancreatic cancer is limited due to side effects such as drowsiness and dizziness but these side effects often vanish during treatment [3].

In severe cancer pain, opioid analgesics are indicated. Even though addiction is rarely a problem in patients with pancreatic ductal adenocancer, due to their severe adverse effects, they should be used as a component of a multidisciplinary strategy that includes every necessary adjuvant analgesic, psychological and social support [3]. The physician should also follow guideline recommendations for opioid use [3, 40–42]. Escalating abdominal pain in spite of increasing doses of opioids may be a

problem in some patients which may be led by opioid induced ileus or constipation or opioid induced hyperalgesia (narcotic bowel syndrome) [3]. These should be treated in the way aforementioned in the secondary reasons of pain section.

It should not be forgotten that there is substantial variance between individuals in both efficacy and side effects of opioids, and that not all patients experience pain relief with narcotics [3]. In such cases an alternative opioid drug may be tried [3]. Methadone may be useful and can be added in small doses to existing opioid therapy [3]. Other treatments that may be tried in stubborn cases also include ketamine, anti-psycotics, clonidine, steroids and cannabinoids [3]. Cannabinoids also have the advantage of being useful appetite stimulants [31] in this pathology which often causes anorexia and cachexia.

In patients with refractory pain, intrathecal drug delivery systems [43] or epidural analgesic administration [44] are effective options. Neurolytic therapies are another alternative for severe, refractory pain, with less adverse effects compared to opioid analgesics [45]. The rationale of neurolytic treatment is to destroy the afferent pathways from pancreas to the brain to reduce pain sensation [3]. In the classic technique, a neurolytic agent is injected around the nerves via a bilateral, percutaneous posterior approach, either guided by fluoroscopy or computed tomography [3]. However, due to the proximity of celiac plexus to the gastric wall, EUS-guided approach provides a safer access to the celiac plexus over percutaneous route. In a retrospective cohort study of 200 participants with pancreatic ductal adenocarcinoma who underwent EUS and percutaneous celiac plexus neurolysis, it has been shown that, both procedures are effective at pain relief, but EUS-guided celiac plexus neurolysis provides more durable pain relief and improved quality of life [46]. Multiple randomized controlled studies have showed that EUS-guided celiac plexus neurolysis provides effective pain relief compared to nonopioid and opioid analgesics [47, 48]. Two meta-analyses showed that celiac plexus neurolysis (either EUS or percutaneous approach) was associated with a significant reduction in narcotic use [45, 47]. Severe complications from EUS-guided celiac plexus interventions are rarely reported and these procedures are considered generally safe. Self-limited diarrhea, abdominal pain and hypotension can be seen. Serious adverse events including paralysis from anterior spinal cord infection, necrotic gastric perforation, and celiac artery thrombosis causing infarction are rare. Due to its efficacy and safety, we recommend early application of EUS-guided celiac plexus neurolysis.

77.7 Conclusions

Pancreatic cancer pain is neuropathic in origin and is a result of highly complicated neuro-cancer and neuro-immune interactions, neuroplastic changes and neural remodeling. These neuropathic alterations correlate with the severity of pain sensation. Understanding this complex mechanism is of translational importance since both pain and neural invasion are independent prognostic factors in this patient group. Many neurotrophic agents, chemokines and various cell types that have a

role in this process are potential targets for ongoing and future research not only to alleviate pain sensation in pancreatic cancer, but also to improve the disease course itself by targeting neural invasion. Until this objective is reached, the conventional means of pain treatment will keep on being the mainstay of analgesia in pancreatic pain. After excluding the secondary reasons of pain, pharmacotherapy for pain in pancreatic cancer should be guided by the WHO analgesic ladder. In refractory pain, intrathecal drug delivery systems, epidural analgesic administration and neurolytic therapies are effective alternatives.

References

1. D'Haese JG, Hartel M, Demir IE, Hinz U, Bergmann F, Buchler MW, et al. Pain sensation in pancreatic diseases is not uniform: the different facets of pancreatic pain. World J Gastroenterol. 2014;20(27):9154–61. https://doi.org/10.3748/wjg.v20.i27.9154.
2. Watson EK, Brett J, Hay H, Witwicki C, Perris A, Poots AJ, et al. Experiences and supportive care needs of UK patients with pancreatic cancer: a cross-sectional questionnaire survey. BMJ Open. 2019;9(11):e032681. https://doi.org/10.1136/bmjopen-2019-032681.
3. Drewes AM, Campbell CM, Ceyhan GO, Delhaye M, Garg PK, van Goor H, et al. Pain in pancreatic ductal adenocarcinoma: a multidisciplinary, international guideline for optimized management. Pancreatology. 2018;18(4):446–57. https://doi.org/10.1016/j.pan.2018.04.008.
4. Ceyhan GO, Bergmann F, Kadihasanoglu M, Altintas B, Demir IE, Hinz U, et al. Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases. Gastroenterology. 2009;136(1):177–86.e1. https://doi.org/10.1053/j.gastro.2008.09.029.
5. Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, et al. Abdominal pain in patients with resectable pancreatic cancer with reference to clinicopathologic findings. Pancreas. 2001;22(3):279–84. https://doi.org/10.1097/00006676-200104000-00009.
6. Tieftrunk E, Demir IE, Friess H, Ceyhan GO. Back pain as a potential indicator of local recurrence in pancreatic cancer. J Surg Case Rep. 2015;2015(10) https://doi.org/10.1093/jscr/rjv127.
7. Caraceni A, Portenoy RK. Pain management in patients with pancreatic carcinoma. Cancer. 1996;78(3 Suppl):639–53. https://doi.org/10.1002/(sici)1097-0142(19960801)78:3<639::Aid-cncr45>3.0.Co;2-x.
8. Demir IE, Ceyhan GO, Liebl F, D'Haese JG, Maak M, Friess H. Neural invasion in pancreatic cancer: the past, present and future. Cancers (Basel). 2010;2(3):1513–27. https://doi.org/10.3390/cancers2031513.
9. Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2015;12(11):649–59. https://doi.org/10.1038/nrgastro.2015.166.
10. Demir IE, Schafer KH, Tieftrunk E, Friess H, Ceyhan GO. Neural plasticity in the gastrointestinal tract: chronic inflammation, neurotrophic signals, and hypersensitivity. Acta Neuropathol. 2013;125(4):491–509. https://doi.org/10.1007/s00401-013-1099-4.
11. Bockman DE, Buchler M, Beger HG. Interaction of pancreatic ductal carcinoma with nerves leads to nerve damage. Gastroenterology. 1994;107(1):219–30. https://doi.org/10.1016/0016-5085(94)90080-9.
12. Nakao A, Harada A, Nonami T, Kaneko T, Takagi H. Clinical significance of carcinoma invasion of the extrapancreatic nerve plexus in pancreatic cancer. Pancreas. 1996;12(4):357–61. https://doi.org/10.1097/00006676-199605000-00006.
13. Ceyhan GO, Schafer KH, Kerscher AG, Rauch U, Demir IE, Kadihasanoglu M, et al. Nerve growth factor and artemin are paracrine mediators of pancreatic neuropathy in pancreatic adenocarcinoma. Ann Surg. 2010;251(5):923–31. https://doi.org/10.1097/SLA.0b013e3181d974d4.

14. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. Annu Rev Neurosci. 2001;24:1217–81. https://doi.org/10.1146/annurev.neuro.24.1.1217.
15. Yan H, Newgreen DF, Young HM. Developmental changes in neurite outgrowth responses of dorsal root and sympathetic ganglia to GDNF, neurturin, and artemin. Dev Dyn. 2003;227(3):395–401. https://doi.org/10.1002/dvdy.10294.
16. Baloh RH, Enomoto H, Johnson EM Jr, Milbrandt J. The GDNF family ligands and receptors – implications for neural development. Curr Opin Neurobiol. 2000;10(1):103–10. https://doi.org/10.1016/s0959-4388(99)00048-3.
17. Andres R, Forgie A, Wyatt S, Chen Q, de Sauvage FJ, Davies AM. Multiple effects of artemin on sympathetic neurone generation, survival and growth. Development. 2001;128(19):3685–95.
18. Ceyhan GO, Giese NA, Erkan M, Kerscher AG, Wente MN, Giese T, et al. The neurotrophic factor artemin promotes pancreatic cancer invasion. Ann Surg. 2006;244(2):274–81. https://doi.org/10.1097/01.sla.0000217642.68697.55.
19. Zhu Z, Friess H, diMola FF, Zimmermann A, Graber HU, Korc M, et al. Nerve growth factor expression correlates with perineural invasion and pain in human pancreatic cancer. J Clin Oncol. 1999;17(8):2419–28. https://doi.org/10.1200/jco.1999.17.8.2419.
20. Ceyhan GO, Michalski CW, Demir IE, Muller MW, Friess H. Pancreatic pain. Best Pract Res Clin Gastroenterol. 2008;22(1):31–44. https://doi.org/10.1016/j.bpg.2007.10.016.
21. Hartel M, di Mola FF, Selvaggi F, Mascetta G, Wente MN, Felix K, et al. Vanilloids in pancreatic cancer: potential for chemotherapy and pain management. Gut. 2006;55(4):519–28. https://doi.org/10.1136/gut.2005.073205.
22. D'Haese JG, Demir IE, Friess H, Ceyhan GO. Fractalkine/CX3CR1: why a single chemokine-receptor duo bears a major and unique therapeutic potential. Expert Opin Ther Targets. 2010;14(2):207–19. https://doi.org/10.1517/14728220903540265.
23. Marchesi F, Piemonti L, Fedele G, Destro A, Roncalli M, Albarello L, et al. The chemokine receptor CX3CR1 is involved in the neural tropism and malignant behavior of pancreatic ductal adenocarcinoma. Cancer Res. 2008;68(21):9060–9. https://doi.org/10.1158/0008-5472.Can-08-1810.
24. Wang K, Demir IE, D'Haese JG, Tieftrunk E, Kujundzic K, Schorn S, et al. The neurotrophic factor neurturin contributes toward an aggressive cancer cell phenotype, neuropathic pain and neuronal plasticity in pancreatic cancer. Carcinogenesis. 2014;35(1):103–13. https://doi.org/10.1093/carcin/bgt312.
25. Demir IE, Schorn S, Schremmer-Danninger E, Wang K, Kehl T, Giese NA, et al. Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. PLoS One. 2013;8(3):e60529. https://doi.org/10.1371/journal.pone.0060529.
26. Vasina V, Barbara G, Talamonti L, Stanghellini V, Corinaldesi R, Tonini M, et al. Enteric neuroplasticity evoked by inflammation. Auton Neurosci. 2006;126–127:264–72. https://doi.org/10.1016/j.autneu.2006.02.025.
27. Buhner S, Schemann M. Mast cell-nerve axis with a focus on the human gut. Biochim Biophys Acta. 2012;1822(1):85–92. https://doi.org/10.1016/j.bbadis.2011.06.004.
28. Ceyhan GO, Demir IE, Rauch U, Bergmann F, Muller MW, Buchler MW, et al. Pancreatic neuropathy results in "neural remodeling" and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer. Am J Gastroenterol. 2009;104(10):2555–65. https://doi.org/10.1038/ajg.2009.380.
29. Ban EG, Brassai A, Vizi ES. The role of the endogenous neurotransmitters associated with neuropathic pain and in the opioid crisis: the innate pain-relieving system. Brain Res Bull. 2019;155:129–36. https://doi.org/10.1016/j.brainresbull.2019.12.001.
30. Nelson KK, Schattner MA, Mendelsohn RB. Methylnaltrexone is safe in cancer patients with peritoneal carcinomatosis. Sci Rep. 2019;9(1):9625. https://doi.org/10.1038/s41598-019-44864-2.
31. Moffat GT, Epstein AS, O'Reilly EM. Pancreatic cancer-a disease in need: optimizing and integrating supportive care. Cancer. 2019;125(22):3927–35. https://doi.org/10.1002/cncr.32423.

32. Perinel J, Adham M. Palliative therapy in pancreatic cancer-palliative surgery. Transl Gastroenterol Hepatol. 2019;4:28. https://doi.org/10.21037/tgh.2019.04.03.
33. Upchurch E, Ragusa M, Cirocchi R. Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction. Cochrane Database Syst Rev. 2018;(5):Cd012506. https://doi.org/10.1002/14651858.CD012506.pub2.
34. Koulouris AI, Banim P, Hart AR. Pain in patients with pancreatic cancer: prevalence, mechanisms, management and future developments. Dig Dis Sci. 2017;62(4):861–70. https://doi.org/10.1007/s10620-017-4488-z.
35. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA. 1995;274(23):1870–3.
36. Holbech JV, Bach FW, Finnerup NB, Brosen K, Jensen TS, Sindrup SH. Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain. 2015;156(5):958–66. https://doi.org/10.1097/j.pain.0000000000000143.
37. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110(3):628–38. https://doi.org/10.1016/j.pain.2004.05.001.
38. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain. 2008;136(1–2):150–7. https://doi.org/10.1016/j.pain.2007.06.033.
39. Olesen SS, Graversen C, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Is timing of medical therapy related to outcome in painful chronic pancreatitis? Pancreas. 2016;45(3):381–7. https://doi.org/10.1097/mpa.0000000000000475.
40. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315(15):1624–45. https://doi.org/10.1001/jama.2016.1464.
41. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13(2):e58–68. https://doi.org/10.1016/s1470-2045(12)70040-2.
42. O'Brien T, Christrup LL, Drewes AM, Fallon MT, Kress HG, McQuay HJ, et al. European Pain Federation position paper on appropriate opioid use in chronic pain management. Eur J Pain. 2017;21(1):3–19. https://doi.org/10.1002/ejp.970.
43. Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, et al. Intrathecal drug delivery systems for cancer pain: an analysis of a prospective, multicenter product surveillance registry. Anesth Analg. 2019;130:289–97. https://doi.org/10.1213/ane.0000000000004425.
44. Kongsgaard U, Kaasa S, Dale O, Ottesen S, Nordoy T, Hessling SE, et al. NIPH systematic reviews: executive summaries. Palliative treatment of cancer-related pain. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH). Copyright (c) 2005 by The Norwegian Institute of Public Health (NIPH). 2005.
45. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev. 2011;(3):Cd007519. https://doi.org/10.1002/14651858.CD007519.pub2.
46. Kambhampati S, Sugar EA, Herman J, Erdek MA, Shin EJ, Laheru D. A comparison of percutaneous and endoscopic-guided celiac plexus block/neurolysis in pancreatic cancer patients. J Clin Oncol. 2018;36(4_Suppl):413. https://doi.org/10.1200/JCO.2018.36.4_suppl.413.
47. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007;102(2):430–8. https://doi.org/10.1111/j.1572-0241.2006.00967.x.
48. Wyse JM, Carone M, Paquin SC, Usatii M, Sahai AV. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol. 2011;29(26):3541–6. https://doi.org/10.1200/jco.2010.32.2750.

Chapter 78
Jaundice in Pancreatic Cancer

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Take Home Messages

- Hyperbilirubinaemia is a frequent event in pancreatic cancer, as diagnosis as during disease evolution.
- When hyperbilirubinaemia is detected, it is necessary to distinguish between prehepatic, posthepatic and hepatotoxic causes.
- In obstructive hyperbilirubinaemia, defined as increased direct bilirubin, drainage by endoscopic retrograde cholangiopancreatography (ERCP) and placement of a stent is recommended.
- There is no clear consensus on the use of chemotherapy in PDAC patients with hyperbilirubinaemia level. Bilirubin >1.5 times UNL is an exclusion criterion in clinical trials, which is the cause of the lack of available data.
- Treatment recommendations should be individualised for each patient.

Future Perspectives

- Randomized studies with chemotherapy (monotherapy or combination) in a situation of hyperbilirubinaemia for robust evidence in this context.
- Stents with longer duration or less risk of superinfection. In some cases, life expectancy of the patient with pancreatic cancer is longer than the useful life of the stent.

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78.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 12th most common cause of cancer and the fourth most common cause of death with an estimation of 432.242 cancer deaths (4.5% of all deaths) worldwide in 2018 [1]. The incidence and mortality rates have not changed in the last decade, it is expected that PDAC will surpass other frequent solid tumours in terms of cancer related death rate by 2030 [2]. The only potential curative treatment is tumor resection, but only 10–20% of patients present at diagnosis with localized disease. The vast majority of patients are diagnosed at advanced stages because the cancer progresses in the asymptomatic phase. PDAC has a dismal prognosis, even patients after curative resection only have an estimated 5-year survival around 20% [3].

Jaundice occurs frequently in PDAC patients, especially in tumours localized in the head leading to subsequent obstruction of the bile duct or by hepatic dissemination.

This chapter focuses on the effects and the clinical management of jaundice in patients that are not amenable for curative intent resection.

78.2 Hyperbilirubinaemia

78.2.1 Pathophysiology and Definition

Bilirubin is a tetrapyrrole produced by the normal degradation of Haemoglobin. When the cell membrane of the erythrocyte breaks macrophages digest the Haemoglobin. This process occurs mainly in the spleen and liver. The macrophages separate the haem and the globin proteins. Secondly, the Haemooxigenase enzyme opens the haem group, resulting in the formation of Biliverdin. It has the green bile characteristic colour. Subsequently, the Biliverdin reductase enzyme processes Biliverdin. The unconjugated Bilirubin reaches the blood and binds to Albumin to be transported to the liver. In the liver, it combines with glucoronic acid to form conjugated Bilirubin. Finally, conjugated Bilirubin is excreted into the bile ducts [4].

There are two forms of Bilirubin: The indirect or unconjungated Bilirubin (IB) is the fraction of bilirubin that has not been metabolised in the liver and is usually found in blood attached to Albumin or freely circulating. The direct or conjugated Bilirubin (DB) has been metabolised in the liver and subsequently secreted into the bile. It is accumulated in the gallbladder for subsequent disposal with digestion.

Hyperbilirubinaemia is defined as as any increase above the normal range, which is 0.3–1.2 mg/dl. When it is detected, a proper differential diagnosis should be performed. There are three main reasons for an elevated serum Bilirubin: prehepatic dysfunction, intrahepatic dysfunction and posthepatic biliary obstruction [5, 6]. Table 78.1 summarises the clinical syndromes and differential diagnosis.

Table 78.1 Reasons for hyperbilirubinaemia

		Bilirubin		
	Unconjugated		Conjugated	
↑ Production	↓ Uptake	Conjugation	Extrahepatic	Intrahepatic
Hemolysis Extravasation Dyserythropoesis	Hepatic blood flow – Congestive heart failure – Portosystemic shunts	Acquired – Liver disease (advanced cirrhosis, chronic hepatitis, Morbus Wilson) – Hyperthyroidism	Instrinsic obstruction – Choledocholithiasis – Cholangiocarcinoma Stricture – Primary sclerosing cholangitis	Infection – Viral hepatitis
	Drugs – Rifampin – Probenecid	Congenital – Morubs Crigler-Najjar – Morbus Gilbert	Extrinsic obstruction – Acquired Immunedeficiency Syndrome cholangiopathy – Parasites	Enviromental – Alcoholic hepatitis – Non alcoholic steatohepatitis – Drugs – Pregnancy
				Ischemia – Shock
				Autoimmune – Primary biliary cirrhosis – Amyloidosis, sarcoidosis

The most frequent causes of hyperbilirubinaemia in patients with PDAC are obstructive extrahepatic cholestasis, intrahepatic cholestasis and hepatotoxicity secondary to chemotherapy.

Obstructive cholestasis is the most frequent situation. It is caused by obstruction of the common bile duct due to a tumor in the pancreatic head. The most common laboratory findings are the elevation of conjugated bilirubin, gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP). Frequently, Alanine aminotransferase (ALT) is elevated as well. This is due to an increased synthesis of plasma ALT in case of any obstruction. The elevated conjugated Bilirubin originates from reflux of Bilirubin glucuronides into plasma due to intra- or posthepatic obstruction.

Intrahepatic cholestasis is usually caused by infiltration of liver parenchyma from metastases. In this situation, ALT and AST are elevated induced by direct parenchymal damage. ALT is more specific for hepatic damage.

Chemotherapy reduces metabolic capacity of the liver and may change hepatic clearance. There is no routine laboratory test to determine the cause of that damage. However, an alteration in the Cytochrome P-450 (CYP-450) reduces drugs clearance [7]. Hepatotropic virus serology should be ruled out in first instance.

High levels of Bilirubin are associated with shorter survival in PDAC [8]. Recent investigations suggest that jaundice impairs anti-tumour immunity and promotes metastasis. In fact, when hyperbilirubinaemia is detected, selecting the proper management is crucial to discriminate whether cholestasis is caused by the tumor or not.

78.2.2 Analytical Confirmation

Jaundice occurs when the Bilirubin level is >2 mg/dl. Complete haematological tests with liver enzymes (ALT, AST, GGT and ALP) lactate dehydrogenase (LDH) and coagulation should be performed. The results can define the type of damage (Table 78.2).

To assess the cause of hyperbilirubinaemia the main imaging techniques are endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) and computed tomography (CT) scans [9]. They allow establishing whether there is extrahepatic dilatation of the biliary tract or liver infiltration. Radiological imaging and endoscopic treatment strategies are extensively discussed elsewhere in this book.

78.3 Management of Hyperbilirubinaemia

78.3.1 Extrahepatic Obstruction

Currently, the treatment of choice for managing obstructive jaundice consists of implanting a biliary stent at the site of obstruction to dilate and permeate the biliary duct.

The type of procedure depends on the expertise of the centres, nevertheless multiple studies comparing surgical versus endoscopic treatment, clearly put endoscopy in front [10].

Endoscopic Retrograde Cholangio Pancreatography (ERCP) is the technique of choice. According to a Cochrane Review [11], endoscopic stenting is successful in 90% of cases with 5% morbidity rate including pancreatitis, bleeding and perforation. If ERCP is not available, contraindicated or technically unsuccessful, a percutaneous drainage should be attempted. In some cases, when the obstruction is at the level of the hilum, percutaneous drainage should be the first option.

Table 78.2 Patterns of damage

Cholestasis	Cytolytic damage
Elevation of GGT and ALP	Elevated ALT and/orAST and LDH
Cause: Intrahepatic or obstructive cholestasis.	*Cause*: Hepatocellular infiltration

A number of different endoscopically delivered stents are available for the purpose of relieving malignant obstruction of the bile duct: Plastic stent, covered self-expandable metal stent (CSEMS) or uncovered self-expandable metal stents (SEMS).

There are no significant differences between the type of stents when successful drainage is achieved but it is very important to be aware of their characteristics in order to establish the correct indication. However, it is well established [12] that metal stents are safe and cost effective in patients in whom chemotherapy is indicated with lower rates of re-intervention and stent dysfunction as well as survival improvement.

We suggest multidisciplinary team meetings to discuss each case based on individual medical history, and prognosis in order to choose the best access and device.

If adequate drainage is not achieved, the situation is similar to intrahepatic cholestasis and the treatment decision must be based on the same principles.

78.3.2 Intrahepatic Cholestasis/Tumor Infiltration

This complex situation excludes the patient from any interventional placement of a stent. The treatment decision should be individualised and discussed in a multidisciplinary team. Different aspects should be taken into account: patient comorbidities; the Bilirubin level, (a level more than five times the upper normal limit—UNL—determines a worse outcome); life expectation and patient symptoms. According to the overall situation a decision has to be made to either initiate oncology treatment or best supportive care.

78.3.3 Treatment in Patients with Hyperbilirubinaemia

The dismal prognosis of metastatic pancreatic tumours was the reason to develop a new therapeutic armamentarium in the last years. Since 1997, Gemcitabine in monotherapy is the standard of care in the metastatic setting [13]. Different combinations have been studied with disappointing results. A small benefit in 12-day median survival with gemcitabine and Erlotinib (Epidermal Growth Factor Receptor - tyrosine kinase inhibitor), gained a regulatory approval [14].

The results from the ACCORD11 study showed a benefit in terms of efficacy with the triplet regimen FOLFIRINOX despite an increase in toxicity. Median overall survival was 11.1 months in the experimental group versus 6.8 months in gemcitabine group (hazard ratio for death, 0.57). Incidences of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea and sensory neuropathy were significantly higher in the FOLFIRINOX group [15]. The doublet with gemcitabine and Nab-paclitaxel showed a benefit in overall survival compared with gemcitabine in monotherapy, 8.7 months versus 6.7 months, respectively. The toxicity profile was more tolerable. Currently, FOLFIRINOX is recommended for the treatment of

metastatic PDAC in patients younger than 75 years-old having a good performance status (ECOG 0) [16].

Nowadays, there is no agreement on the use of chemotherapy in PDAC with hyperbilirubinaemia [17]. Patients with abnormal (more than 1.5 or 2 UNL) serum liver biochemical test are excluded in trials. This is the reason for the lack of available data in this population with the exception of single case reports. The experience with chemotherapy combinations is even lower. Hence, it is important to emphasize that any recommendation for treatment with chemotherapy (in monotherapy or combination) must be based on an individualized case-by-case risk/benefit analysis.

78.3.4 Gemcitabine

Gemcitabine is a broad-spectrum antimetabolite and deoxycytidine analogue with antineoplastic activity. The drug is inactivated in the liver and can increase transaminases and Bilirubin level. It is mandatory to assess hepatic function prior to initiation of Gemcitabine and periodically during treatment. A phase II trial evaluated 43 patients, 20 with hepatocellular carcinoma and 23 pts. with cholangiocellular carcinoma. Eighteen patients with hepatocellular carcinoma had underlying liver cirrhosis. The most frequent side effects were thrombocytopenia in the latter group (30% grade 3/4) whereas nausea and neutropenia in cholangiocellular carcinomas cohort was most commonly reported [18]. A prospective analysis for dose escalated of Gemcitabine assigned 40 patients in three cohorts: group I. with AST $\leq \times 2$ UNL and Bilirubin <1.6 mg/dl; group II with Bilirubin 1.6–7.0 mg/dl and group III. with creatinine level 1.6–5.0 mg/dl and normal liver function. The conclusion of that small study was that use Gemcitabine with elevations in AST level was safe making no dose reduction necessary. Nevertheless, patients with elevated bilirubin levels have an increased risk of hepatic toxicity, therefore a dose reduction was recommended [19].

On the other hand, a study from Japan concluded that the initial dose reduction of Gemcitabine as monotherapy for the treatment of biliary tract or pancreatic cancer in patients with liver dysfunction is unnecessary. Even in patients who have severe liver dysfunction (bilirubin level 3.0- to 10.0-fold higher than ULN with any AST/ALT levels) the dose 1000 mg/m^2 is safe, provided that obstructive jaundice is well managed [20].

78.3.5 Nab-Paclitaxel

Nab-Paclitaxel is an albumin-bound Paclitaxel that eliminates the need for cremophor EL (polyoxyethylated castor oil). This drug is metabolised in the liver and eliminated via biliary secretion (70%). Some studies investigated the pharmakocinetics and toxicity of Paclitaxel in patients with liver dysfunction and hyperbilirubinaemia. A prospective analysis in patients with severe hepatic dysfunction

(transaminase serum level higher than ×10 UNL and Bilirubin serum levels high than ×5 UNL) the administration of Paclitaxel 70 mg/m^2 was well tolerated and safe [21].

Another pilot study assigned the dose of 130, 200 or 260 mg/m^2 of nab-Paclitaxel every 3 weeks in 30 patients with elevated Bilirubin and ALT. Treatment-related grade 3 hyperbilirubinaemia and elevated ALT was observed in patients receiving 130 and 260 mg/m^2. There was an inverse correlation between drug clearance and level of Bilirubin. Nevertheless, nab-Paclitaxel has an adequate tolerability profile in patients with liver dysfunction [22]. A recent meta-analysis recommended a reduction of 20% of the dose of nab-Paclitaxel in patients with high level of Bilirubin (total Bilirubin >1.5 to <5 ULN). The reduction is necessary to avoid an increase in drug exposure in this population [23].

An ongoing study is analysing safety and pharmaco-kinetics profile of nab-Paclitaxel and Gemcitabine in patients with PDAC and cholestastic hyperbilirubinaemia. A comparison of different doses of nab-Paclitaxel (100 mg/m^2 versus 75 mg/m^2) and Gemcitabine (800 mg/m^2 versus 600 mg/m^2) is being tested. Final results are awaited at time of writing [24].

78.3.6 5-Fluorouracil (5-FU)

5-FU is an antimetabolite, which interferes with the synthesis of DNA and RNA. A phase I study evaluated 64 patients (16 in a cohort with Bilirubin >1.5 but <5 mg/dl with normal creatinine and 27 pts. in the cohort with Bilirubin ≥5 mg/dl with normal creatinine. 11 patients in total were diagnosed with pancreatic cancer. They found no evidence that patients with high creatinine or bilirubin levels suffered higher toxicity with 5-FU [25]. There is not much clinical evidence for this scenario in PDAC.

Another recent study observed that the treatment with the combination of Oxaliplatin, 5-FU ± a monoclonal antibody was feasible and may derive clinical benefits in patients with liver dysfunction caused by gastrointestinal cancer metastasis [26].

78.3.7 Oxaliplatin

Oxaliplatin is a platinum compound. This compound exerts its cytotoxic effect via covalent adducts with cellular DNA. It is not cell-cycle specific, has a renal elimination and a non-enzymatic liver metabolism [27]. A randomised trial has shown a significant benefit in overall survival in 2.6 months with 5-FU, folinic acid and Oxaliplatin compared with 5-FU in monotherapy as second line treatment (Hazard ratio of death 0.66) [28]. These results have not been confirmed in recent data. A meta-analysis compared monotherapy based on 5-FU with the combination of 5-FU plus Oxaliplatin in progressive patients after treatment with Gemcitabine and

Nab–Paclitaxel chemotherapy. Although the result showed a modest benefit in progression-free survival, this benefit did not translate into survival advantage [29]. Similar results have been published with a modest efficacy in second line with 5-FU and Oxaliplatin compared with 5-FU monotherapy [30]. In this context, the combination with Oxaliplatin is not the best option based on the guidelines, but it can be regarded a safe option in patients with hyperbilirubinaemia who cannot receive another treatment [26, 31].

78.3.8 Nanoliposomal Irinotecan (Nal-IRI)

Irinotecan is a semi-synthetic derivative of CPT, a Topoisomerase-I inhibitor. It is metabolised in the liver by carboxylesterases to SN-38. SN-38 is excreted in the bile and undergoes extensive enterohepatic re-circulation which is the cause of the main side effects [27]. The detoxification pathway of SN-38 is driven by the hepatic uridine diphosphate glucuronosyltransferase (UGT) [32]. In patients with hepatic dysfunction a significant pharmacokinetic variability occurs [33]. A study in patients with colorectal cancer observed that the Bilirubin plasma levels were much higher in patients with UGT homozygosity causing more risk of neutropenia [34]. A phase I study showed that treatment of patients with high level of Bilirubin (×3 UNL) should only be done with a dose reduction [35].

Recently, the NAPOLI-1 trial demonstrated a significant survival benefit of nal-IRI + 5-FU/LV compared with 5-FU alone in second line [36].

Nanoliposomal Irinotecan (nal-IRI) is a novel formulation of Irinotecan. It has a favourable pharmacokinetic profile and biodistribution due to encapsulating the drug molecule within long-circulating liposome-based nanoparticles [37].

To sum up, in patients with hyperbilirubinaemia and in Gilbert's syndrome the dose of Irinotecan should be reduced [27]. There is no clinical data that included patients with hyperbilirubinaemia and nal-IRI. Irinotecan and nal-IRI should therefore be administrated carefully in this population.

In an attempt to guide therapeutic recommendations for chemotherapy treatment in PDAC patients with jaundice, a Spanish multidisciplinary working group [17] published recommendations based on the level of Bilirubin in patients with biliary stents (Table 78.3).

In patients with jaundice due to liver parenchymal damage or with an inefficient stent, all drugs must be used with caution and combinations with Irinotecan are not recommended if Bilirubin levels are above 2 UNL.

78.4 Conclusion

Despite the efforts for new therapeutic strategies, the clinical outcome of patients with pancreatic cancer is unsatisfactory. The detection of hyperbilirubinaemia requires a meticulous differential diagnosis. Actually, PDAC can debut with high

Table 78.3 Treatment recommendations and dose adjustement

Total Bilirubin levels	Bilirubin < 1.5 UNL	Bilirubin = 1.5–5 UNL	Bilirubin > 5 UNL
Gemcitabine	100% dose	80–100% dose	Not recommended
Gemcitabine + Nab paclitaxel	100% dose of both drugs	80% Nab-Paclitaxel 100% GEM	Not recommended
Nal-IRi + 5-FU	100% dose	Not recommended	Not recommended
5-FU + Leucovorin[a]	100% dose	Up to 100% dose	Individualize: Use with caution
5-FU + Oxaliplatin	100% dose	Up to 100% dose	Individualize: Use with caution
FOLFIRINOX	100% dose of all the drugs	Not recommended	Not recommended

Adapted form: Álvarez et al. [18]
[a]Dose of 5-Fu 2600 mg/m^2/24 h continuous infusion once a week + LV

level of Bilirubin or can be detected during the disease evolution. When appearing, it is important to differentiate the cause and try to determine the best therapeutic option. Obstructive hyperbilirubinaemia has a better prognosis if drainage by ERCP and placement with a stent is possible. However, there is no consensus about chemotherapy recommendations. The selection of the patient is crucial to determine the best therapeutic option. The lack of phase III trials in this population is the reason for an individualized therapeutic management. The previous recommendations are based on monotherapy drugs. Furthermore, the NCCN and ESMO guidelines in pancreatic cancer recommended a combination therapy due to the aggressiveness of this disease. The clinical data justifies the administration of two or three drug of chemotherapy in order to obtain the best response rate. Patients with pancreatic cancer and hyperbilirubinaemia should be evaluated carefully. Each drug may be monitored individually according to Bilirubin level and its evolution, whether using bile drainage or not.

Therefore, guidelines of chemotherapy to treat this population need to be developed.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
3. Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, et al. Multiinstitutional validation study of the American Joint Commission on cancer (8th edition) changes for T and N staging in patients with pancreatic adenocarcinoma. Ann Surg. 2017;265(1):185–91.
4. Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. The lancet oncology. 2008;9(11):1092–101.
5. Sherwood RA, Bomford A. Assessment of hepatic function and investigation of jaundice. Clinical biochemistry E-book: With Expert Consult access. 2014. p. 231.

6. Hirschfield GM, Heathcote EJ, Gershwin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology. 2010;139(5):1481–96.
7. Bibi Z. Role of cytochrome P450 in drug interactions. Nutr Metab. 2008;5(1):27.
8. Strasberg SM, Gao F, Sanford D, Linehan DC, Hawkins WG, Fields R, et al. Jaundice: an important, poorly recognized risk factor for diminished survival in patients with adenocarcinoma of the head of the pancreas. HPB. 2014;16(2):150–6.
9. Iwashita T, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. Clin J Gastroenterol. 2014;7(2):94–102.
10. Glazer ES, Hornbrook MC, Krouse RS. A meta-analysis of randomized trials: immediate stent placement vs. surgical bypass in the palliative management of malignant biliary obstruction. J Pain Symptom Manage. 2014;47(2):307–14.
11. Moss AC, Morris E, MacMathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev. 2006;(2):CD004200.
12. Dumonceau JM, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline—updated October 2017. Endoscopy. 2018;50(09):910–30.
13. Burris H, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
14. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960–6.
15. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
16. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
17. Álvarez R, Carrato A, Adeva J, Alés I, Prados S, Valladares M, et al. Management of hyperbilirubinaemia in pancreatic cancer patients. Eur J Cancer. 2018;94:26–36.
18. Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepatogastroenterology. 2001;48(39):783–9.
19. Venook AP, Egorin MJ, Rosner GL, Hollis D, Mani S, Hawkins M, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol. 2000;18(14):2780–7.
20. Shibata T, Ebata T, Fujita KI, Shimokata T, Maeda O, Mitsuma A, et al. Optimal dose of gemcitabine for the treatment of biliary tract or pancreatic cancer in patients with liver dysfunction. Cancer Sci. 2016;107(2):168–72.
21. Briasoulis E, Karavasilis V, Tzamakou E, Piperidou C, Soulti K, Pavlidis N. Feasibility study and pharmacokinetics of low-dose paclitaxel in cancer patients with severe hepatic dysfunction. Anticancer Drugs. 2016;17(10):1219–22.
22. Biakhov MY, Kononova GV, Iglesias J, Desai N, Bhar P, Schmid AN, et al. nab-Paclitaxel in patients with advanced solid tumors and hepatic dysfunction: a pilot study. Expert Opin Drug Saf. 2016;9(4):515–23.
23. Chen N, Li Y, Ye Y, Palmisano M, Chopra R, Zhou S. Pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with solid tumors: disposition kinetics and pharmacology distinct from solvent-based paclitaxel. J Clin Pharmacol. 2014;54(10):1097–107.
24. Riess H, Kunzmann V, Philip PA, Seufferlein T, McGovern DMT, Chen P. A phase I safety and pharmacokinetic (PK) study of nab-paclitaxel (nab-P) plus gemcitabine (Gem) for patients (pts) with advanced pancreatic cancer (APC) who have cholestatic hyperbilirubinemia (CH) secondary to bile duct obstruction. 2016;34(4_Suppl)

25. Fleming GF, Schilsky RL, Schumm LP, Meyerson A, Hong AM, Vogelzang NJ. Phase I and pharmacokinetic study of 24-hour infusion 5-fluorouracil and leucovorin in patients with organ dysfunction. Ann Oncol. 2003;14(7):1142–7.
26. Quidde J, Azémar M, Bokemeyer C, Arnold D, Stein A. Treatment approach in patients with hyperbilirubinemia secondary to liver metastases in gastrointestinal malignancies: a case series and review of literature. Ther Adv Med Oncol. 2016;8(3):144–52.
27. Sessa C, Gianni L, Garassino M, van Halteren H. ESMO handbook of clinical pharmacology of anti-cancer agents. Viganello-Lugano: ESMO; 2012.
28. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32(23):2423–9.
29. Sonbol MB, Firwana B, Wang Z, Almader-Douglas D, Borad MJ, Makhoul I. Second-line treatment in patients with pancreatic ductal adenocarcinoma: a meta-analysis. Cancer. 2017;123(23):4680–6.
30. Lee K, Bang K, Yoo C, Hwang I, Jeong JH, Chang HM. Clinical outcomes of second-line chemotherapy after progression on nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic adenocarcinoma. Cancer Res Treat. 2020;52(1):254–62.
31. Elsoueidi R, Craig J, Mourad H, Richa EM. Safety and efficacy of FOLFOX followed by cetuximab for metastatic colorectal cancer with severe liver dysfunction. J Natl Compr Cancer Netw. 2014;12(2):155–60.
32. Bai Y, Wu HW, Ma X, Liu Y, Zhang YH. Relationship between UGT1A1* 6/* 28 gene polymorphisms and the efficacy and toxicity of irinotecan-based chemotherapy. Onco Targets Ther. 2017;10:3071.
33. Fujita KI, Sparreboom A. Pharmacogenetics of irinotecan disposition and toxicity: a review. Curr Clin Pharmacol. 2010;5(3):209–17.
34. Rouits E, Charasson V, Pétain A, Boisdron-Celle M, Delord JP, Fonck M, et al. Pharmacokinetic and pharmacogenetic determinants of the activity and toxicity of irinotecan in metastatic colorectal cancer patients. Br J Cancer. 2008;99(8):1239.
35. Venook AP, Enders Klein C, Fleming G, Hollis D, Leichman CG, Hohl R, et al. A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. Ann Oncol. 2003;14(12):1783–90.
36. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;87(10018):545–57.
37. Drummond DC, Noble CO, Guo Z, Hong K, Park JW, Kirpotin DB. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. Cancer Res. 2006;66(6):3271–7.

Chapter 79
Palliative Endoscopic Therapy in Pancreatic Cancer

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Take Home Messages
- Plan timing and sequence so that the least amount of sessions ensures the maximal benefit
- Evaluate benefits, risks, alternatives and rescue techniques before starting
- Do not use uncovered metal stents before definitive diagnosis
- Avoid follow up interventions due to the use of plastic stents in palliative cases

Pearls and Pitfalls
- Plan for definitive solutions—avoid implanting plastic stents in palliative cases to spare the patient possible complications and follow up procedures
- In hilar strictures, aim at draining minimum 50% of liver volume to achieve a significant drop in serum bilirubin
- Adapt to patient's needs—there are different goals in palliative cancer treatment

Future Perspectives
- Ideal timing and manner of secondary interventions over EUS-guided fistula
- Optimization of long term patency of EUS-BD fistulas with and without indwelling stent
- EUS guided therapeutic oncologic interventions, especially in combination with ERCP

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79.1 Introduction

Endoscopic palliation in pancreatic cancer patients is an evolving topic due to the rising incidence and longer survival rates of patients diagnosed in a metastasized stadium [1]. In the early days of endoscopic interventions in pancreatic cancer the so called “double duct sign” was a diagnostic finding highly suggestive for a neoplastic process in the pancreatic head in endoscopic retrograde cholangiopancreatography (ERCP), that we see less frequent today. An X-ray picture of a double duct sign is displayed in Fig. 79.1. This has to do with devolvement of less invasive imaging procedures that can give diagnostic information on soft tissue and ductal anatomy, so that the diagnostic value of ERCP imaging has been decreasing quickly, while interventional possibilities and procedures are evolving quickly [2]. The expansive growth of malignant tumors of the pancreas causes typical and less typical problems that often can be addressed via endoscopic procedures (Fig. 79.2).

79.2 Biliary Obstruction

Patients with biliary obstruction due to malignant disease, in contrast to benign causes, often present with rather asymptomatic weight loss, moderate pain and/or yellow color of skin or eyes that, due to the slow development often is noted by relatives or friends rather than the patient self. Due to this character, malignant jaundice is usually noted in later states with extensive widening of the biliary ducts and very high liver tests. The jaundice usually arises due to compression or infiltration of the biliary system by the tumor or metastases that cause obstruction of biliary flow. This can be divided in extrahepatic and intrahepatic or combined biliary obstruction. In the palliative setting, biliary drainage is indicated to relief symptoms such as itching

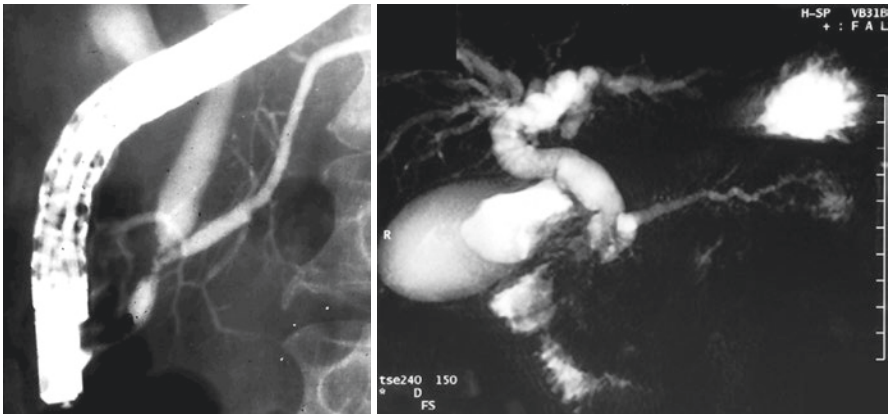

Fig. 79.1 X-ray picture from an ERCP showing a typical double duct sign

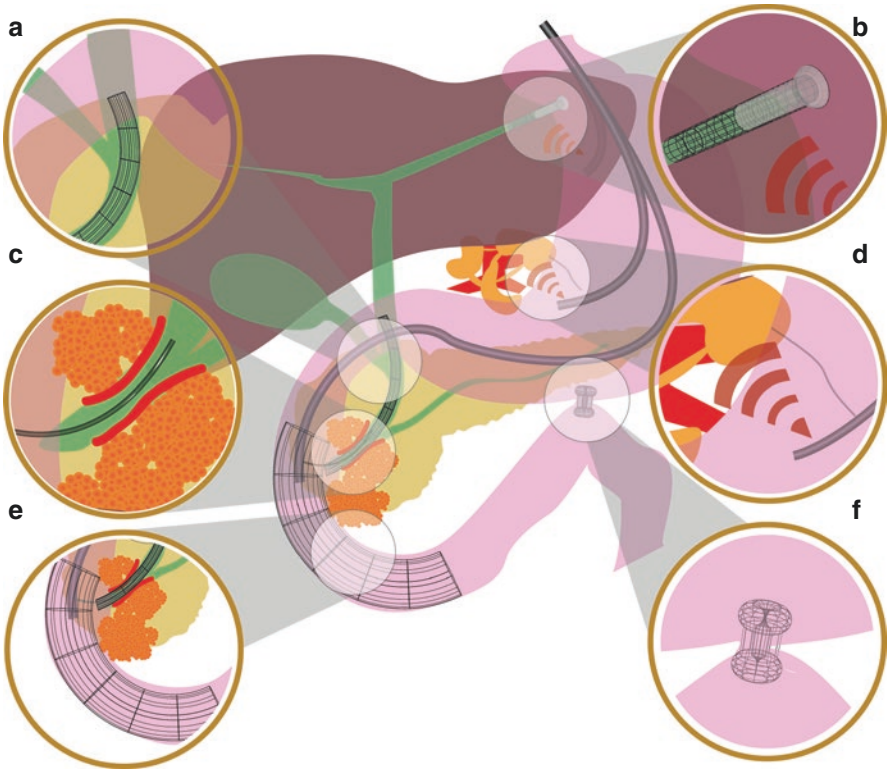

Fig. 79.2 Illustration of endoscopic palliation in pancreatic cancer. (**a**) Classic biliary SEMS. (**b**) EUS-BD via hepatogastrostomy. (**c**) Intraductal radiofrequency ablation. (**d**) EUS guided celiac plexus intervention. (**e**) Duodenal stent. (f) EUS guided gastro-enterostomy with indwelling LAMS

or dyspepsia, but also to prevent liver failure and secondary problems such as altered blood coagulation and accelerated weight loss due to impaired enterohepatic circulation. Furthermore, biliary drainage is often performed to allow palliative cytostatic therapy in patients with high serum bilirubin levels.

79.3 ERCP (Endoscopic Retrograde Cholangio-Pancreatography)

Palliative endoscopic biliary drainage via ERCP is the first line approach and should be preferred over percutaneous or surgical decompression procedures because of clear evidence in favor of ERCP [3]. Still, also ERCP has a considerable risk profile and can lead to severe complications and even death especially in elderly, frail, comorbid patients with malignancy [4, 5].

Extrahepatic biliary obstruction is usually caused by obstruction of the distal portion of the common hepatic duct that runs through the pancreatic head. Mostly, this situation can be addressed with a single stent that covers this area, while in the case of hilar or intrahepatic obstruction, the situation becomes more complex and difficult to resolve. Modern guidelines recommend the implantation of self expanding metal stents (SEMS) for all palliative cases [3, 6] to assure permanent intervention free drainage, while earlier guidelines referred to estimating the patient's life expectancy to decide if the use of a SEMS would be cost effective compared against plastic stents [7, 8]. Both a plastic stent and a fully covered SEMS are displayed in Fig. 79.3.

Life expectancy has become more difficult to estimate under modern cytostatic treatment regimens, to which a subgroup of patients responds relatively well [9]. Additionally, time to stent occlusion of plastic stents in the biliary tract is usually estimated to be between 3 to 6 months [10]. Furthermore, there are hints that plastic stents occlude even earlier in pancreatic cancer, for which reason they should be avoided [11].

Due to their woven expanding metal construction, SEMS are small enough to be implanted in most strictures, even if they are tight and in a difficult position. By applying long term moderate expansion force to the stricture and opening to a much larger inner diameter, they allow patency drainage with relatively rare complications. SEMS can be covered and uncovered and both show similar long term patency rates that exceed the life expectancy of the majority of palliative patients with pancreatic cancer [12, 13]. However, nowadays, some patients live long enough to experience stent dysfunctions due to the increasing survival times.

In uncovered SEMS, dysfunction relates mainly to stent occlusion by tumor ingrowth, while in covered SEMS, higher rates of tumor overgrowth and stent migrations are reported [12–15]. Partially covered SEMS design has the aim to unite advantages of both covered and uncovered SEMS, but general statements on this heterogeneous group of stents are difficult. Uncovered SEMS have the advantages of virtually never dislocating and not obstructing branching ducts, which are important in patients with hilar obstruction or anatomical variations.

The risk for cholecystitis caused by covered SEMS due to occlusion of the cystic duct orifice has been discussed extensively, but it seems of little or no relevance [16, 17]. It cannot be emphasized enough, that uncovered SEMS are usually not removable and should therefore not be implanted in patients with unclear dignity of disease.

Histologically confirmed malignancy in the state of palliation should be confirmed before implanting non removable stent models, since numbers as high as 5–10% of cases of misjudged benign disease have been describe in the follow up [18]. Virtually every larger center has a story to tell about implantation of uncovered SEMS in misinterpreted rare or unexpected curable diseases that often include chronic pancreatitis, autoimmune pancreatitis and/or cholangitis and lymphoma. In these situations, the most common endoscopic approach is to implant a covered SEMS in the uncovered one for later removal of both stents [19], but this rescue method does not always succeed. Alternatives include rare rescue procedures involving forceps, snares, balloons, Soehendra lithotrypters and thermoablation

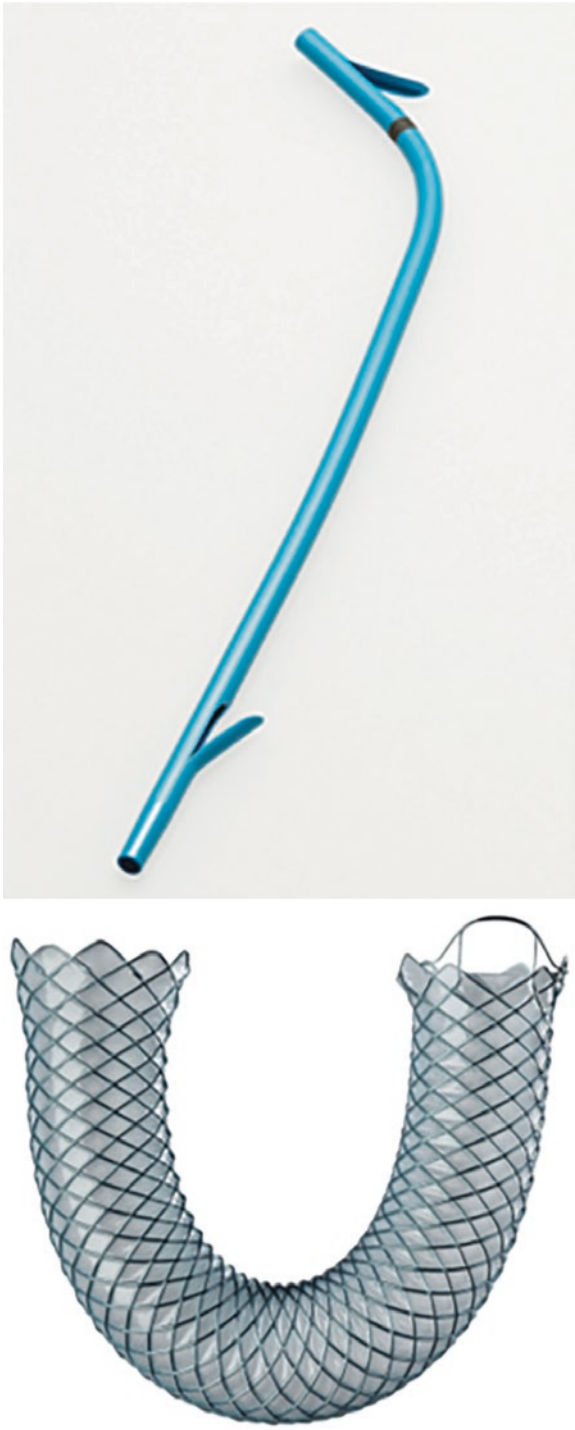

Fig. 79.3 Photograph of a biliary plastic stent (above) and fully covered biliary SEMS (below). (Material provided courtesy of Boston Scientific. Copyright 2019 © Boston Scientific Corporation or its affiliates. All rights reserved)

techniques that should be performed in expert hands after careful evaluation and consideration of possible complications [20].

When evaluating cases with malignant hilar or intrahepatic stenoses for drainage ERCP, at least 50% of the liver volume should seem reasonably accomplishable. Further, only ducts that will be drained during the intervention should be opacified to avoid complications [21, 22]. This can easily develop into a 'Catch-22' situation, since contrast injection is unselective, before a certain area has been accessed and a duct cannot be seen in normal ERCP before opacification. Still, good knowledge of available pre-interventional radiology and very careful contrast injection can help avoiding complications in these often complex procedures.

When a SEMS passes over side branches, it is crucial to not occlude them to avoid complications such as incomplete or insufficient drainage, cholangitis and abscess formation [3] For this reason, covered SEMS can almost never be used in these cases and plastic stents should be avoided if possible because of their shorter patency. Thus, uncovered SEMS are the metal stent of choice in the setting of hilar obstructions or atypical anatomical variations. To achieve bilateral drainage, stents can be placed in side-by-side or SEMS through SEMS techniques. Advancements in design lately even allow have two SEMS in the endoscope at the same time, allowing easy and precise deployment in side-by-side technique.

79.3.1 Risks and Benefits

In clinical practice, interventionalists might sometimes feel obliged to go for a trial for sufficient drainage for the patient to receive chemotherapy, even if the chances for clinical success are not very high. Clinical success in these cases would mean that the bilirubin levels lower sufficiently for the patient to receive palliative chemotherapy. Chances for clinical success are most difficult in cases with hilar strictures, in which more than one ductal structure is obstructed and complete drainage of all opacified segments might not be achieved and patients are at higher risk for complication and more often need additional or rescue percutaneous drainage [23, 24]. Additional confounding factors when estimating the chances for success might be the degree of parenchymal infiltration by the tumor, ongoing or recent infections as well as preexisting liver damage, but study data on how to transduce such factors into reliable conclusions are lacking. In cases with no preexisting liver disease, drainage of 50% of the liver volume was necessary to achieve a significant drop in bilirubin [21, 22]. Most patients opt for a drainage try even after hearing about possible risks or concerns, because it is the only chance for receiving a life prolonging therapy in an otherwise hopeless situation. With only weeks of lifetime at stake without therapy, the risk of severe or even fatal complications seems less repelling. As an endoscopist in this situation, it is important to be aware of the risks and clearly communicate possible complications and limitations.

On the other hand, going for a risky try is not always wrong if all persons involved have been informed and support the concept. In cases that do not seem resolvable endoscopically, percutaneous drainage techniques may be applied as an alternative first line approach, either alone, in combination with ERCP or as a rescue method to avoid cholangitis in case opacified ducts cannot be drained [3].

79.3.2 Type of Stents Used in ERCP Drainage

The use of plastic stents might be tempting because of easy and quick implantation, corrigible stent position, but presumably also because of high costs of SEMS put pressure on the budget of endoscopy units. Stent costs vary according to manufacturer, distributor and country of sale, but in general SEMS cost approximately 15–40 times as much as plastic stents [25]. Therefore, even in highly developed countries like Germany or the Netherlands, an ERCP with single SEMS implantation has almost double the cost of an ERCP using a single plastic stent [26, 27]. When implanting several SEMS during ERCP, the procedure can even develop into a financial loss, in contrast to ERCP with plastic stents and a follow up ERCP after 3 month [11]. Stent costs obviously do affect the direct procedural cost of an ERCP [26, 27], but are not a relevant factor in the total costs of palliative patient care [8]. An overview of stent characteristics and rough price estimates are given in Table 79.1.

The use of plastic stents, in case of stent occlusion, can result in a wide range of undesired effects besides an additional ERCP, such as additional diagnostic imaging, radiation, antibiotic treatment and longer hospital stay with all adjacent costs and patients stress [8]. Especially under aggressive chemotherapy, stent occlusion and cholangitis may initially be masked because of poor immune response, but can in the further course lead to severe cholangitis, delayed or discontinued chemotherapy and even death [28].

In case of occlusion of plastic stents, the occluded stent is usually extracted and a new stent is implanted and the same applies for extractable SEMS. In case an

Table 79.1 Properties of different stent types used in endoscopic palliation of pancreatic cancer

Stent type	Diameter (Charrière)	Approximate costs (euro)[a]	Indwelling time
Plastic stent	7–11.5	50–100	3 months
Covered biliary SEMS	18–30[b]	700–1000	6–12 months[c]
Uncovered biliary SEMS		700–1000	Unlimited
LAMS	18–60[b]	1000–3500	<8 weeks[c]
Duodenal SEMS	60–90[b]	700–1300	Unlimited

[a]Depend on manufacturer, retailer, country and number of purchase
[b]Fully expanded
[c]Manufacturer recommendation for save removal

unextractable SEMS occludes, ESGE mentions both plastic and metal stents for stent-in-stent placement in the indwelling SEMS [3]. This treatment can be combined with intraductal radiofrequency ablation to reestablish a wider stent lumen, but usually is still combined with a stent-in-stent placement at the end of the RFA procedure to avoid secondary complications such as bleeding or duct occlusion by tumor debris [29].

79.3.3 EUS Guided Biliary Drainage (EUS-BD)

In cases in which the papilla Vateri cannot be reached or cannulated, endosonographic procedures have evolved as an alternative endoscopic approach to the transpapillary ductal access. When EUS-BD is used as a salvage strategy after transpapillary approach has failed, higher complication rates compared to ERCP have been found in a meta-analysis [30]. With increasing experience of both single endoscopists and centers in EUS-BD, as well as technical evolutions in stent design, complication rates have been shown to decrease [31, 32]. When ERCP and EUS-BD performed by expert hands are compared in a randomized prospective way, widely equivalent results in malignant biliary obstruction have been found [33]. Possible advantages of EUS-BD over ERCP are the much smaller risk of causing pancreatic irritations and thereby pancreatitis. No clear advantage of one access route over the other has been identified and the choice in mainly influenced by the patient's anatomy and local expertise and preference [34, 35].

While first EUS-BD procedures have been performed using biliary SEMS or even plastic stents, more recently the use of lumen opposing metal stents (LAMS) for extrahepatic drainage procedures has been adopted from the original indication of management of fluid collections. LAMS are a special form of SEMS that are characterized by a short cylindrical stent body and large collars, as seen in Fig. 79.4, for opposing the lumen of two cavities and sealing the newly created anastomosis

Fig. 79.4 Photograph of an expanded LAMS on electrocautery delivery system. (Material provided courtesy of Boston Scientific. Copyright 2019 © Boston Scientific Corporation or its affiliates. All rights reserved)

tight which helps to prevent bleeding, stent obstruction and dislocation [36, 37]. Second generation LAMS offer the possibility of single step electrocautery stent insertion without time consuming and possibly dangerous device exchanges over wire [30, 36, 38]. For intrahepatic EUS-BD via hepatogastrostomy, a covered expandable stent portion is desired for bridging and sealing the peritoneal gap. As in hilar stenting, the intrahepatic portion should not occlude branch ducts. Finally, the stent should not dislocate from both the intrahepatic and intragastric position. Therefore, mostly specially designed SEMS with an uncovered intrahepatic portion, a covered extrahepatic part and a flared end in the stomach are used to prevent leakages and dislodgements [39, 40].

In EUS-BD, once the stent is placed, a stable fistula forms over time [30]. First studies show that a late stent dislocation from such a fistula does not necessarily lead to complications [41]. Bypassing the tumor obstruction with a fistula may be a concept that takes away the need for permanently indwelling foreign bodies with maximal patency. However, further evaluation is needed in the future to validate this concept and establish time intervals for save stent removal.

79.4 Pancreatic Drainage

Limited evidence exists on the positive effects of ductal decompression on pain and quality of life in pancreatic cancer patients [42–45]. Although the pathophysiological concept is convincing and the equipment to perform this procedure is easily available, pain in pancreatic cancer is usually multifactorial and is rather driven by events such as infiltration of the peripancreatic neuronal structures than by high parenchymal pressure due to ductal obstruction [46, 47]. Indication for pancreatic ductal access in pancreatic cancer is limited to indefinite diagnosis and rare cases of recurrent pancreatitis due to obstruction of the pancreatic duct [48]. EUS guided ductal access, analog to EUS-BD, has been described for pancreatic duct drainage [48, 49].

79.5 Gastroduodenal Obstruction

79.5.1 EUS Guided Enteral Anastomoses

Advanced pancreatic cancer is the most common cause of gastric outlet or duodenal obstruction in the western world [50]. Placement of a duodenal SEMS is an established alternative to surgical gastro-enterostomy. Retrospective studies show equal effectiveness with shorter hospitalization and earlier oral food intake and chemotherapy start for the endoscopic approach [35, 51, 52]. Possible downsides of duodenal stenting are stent migrations, dietary limitations, tumor ingrowth, bleedings

or perforations. If a duodenal stent is placed over the ampullary region, transpapillary and transduodenal interventions might be impeded and secondary problems, such as obstruction of indwelling biliary stents by compression or food impaction can occur [53, 54]. Usually uncovered SEMS are used because of the high risk of dislocation. A developing endoscopic alternative to duodenal stenting is EUS guided gastro-enterostomy that is addressed below.

79.6 EUS-Guided Palliative Interventions in Pancreatic Cancer

79.6.1 EUS Guided Enteral Anastomoses

There are several technical variations to establish EUS guided gastro-enterostomy that range from direct punction of the purely endosonographically identified target bowel segment, over balloon assisted punction with either single balloon or specially developed double balloon catheters to ultra slim scope assisted technique [55, 56] In all cases, large diameter LAMS are used [56]. Recent multicenter studies on this topic revealed lower complication rates when compared to surgical gastro-enterostomy with similar clinical success rates [57, 58], making EUS gastro-enterostomy a promising alternative to both gastroduodenal stenting and surgical gastro-enterostomy. Similarly, anastomoses between luminal structures other than the duodenum in close relation are possible, that are useful especially in patients with altered anatomy, to perform different interventions in the otherwise hard to reach excluded stomach and duodenum [59, 60]. These cases might seem exotic, but with the steady rise of obesity and bariatric interventions, will gain importance in the future as an alternative to laparoscopically assisted ERCP in patients with gastric bypass surgery [61, 62]. Before secondary interventions, such as ERCP, are performed over these fistulas, a stable channel should have formed to minimize the risk of complications. Expert opinion on the minimal interval for a stable fistula to form is 2–4 weeks, study data on this topic are missing. If an urgent intervention over a newly established fistula is necessary, endoscopic clipping and stitching methods to fix the LAMS in place have been described to reduce the risk of stent dislodgement [63], but nevertheless expertise and equipment for endoscopic complication handling in case of stent dislodgement are crucial.

79.6.2 EUS Guided Celiac Plexus Intervention for Pain

Celiac plexus interventions have been performed for a long time. EUS-guided celiac plexus neurolysis is safer than the previously used techniques and may give relieve to 70–80% of patients suffering from pain caused by pancreatic cancer [64]. The procedure carries a risk of mostly mild acute adverse events in about 40% of the

patients, such as transient worsening of pain, diarrhea and hypotension [65]. In rare cases, severe adverse events such as bleeding ischemic and infectious complications can occur [64]. The use of local anesthetics is only effective for a limited period of time. Thus, neurodestructive agents like alcohols or phenols are the preferred approach in pancreatic cancer patients, with ethanol being the preferred agent [64]. Bilateral injections are probably more effective than unilateral approaches [64]. The relatively new technique of EUS guided radiofrequency ablation of the celiac axis shows promising results, but further experience has to be gained [66].

79.6.3 EUS Guided Placement of Therapeutic Agents

This is a field that is developing in many directions. The injection of chemotherapeutics, tumorlytic agents as well as EUS guided radiofrequency tumor ablation and delivery of radioactive seeds for brachytherapy as well as photodynamic therapy have been reported [67]. As for today, none of these methods been widely established in clinical practice outside of clinical trials and further research is needed.

79.7 Timing of Intervention

With newly emerging possibilities, an increasing number of endoscopic interventions beyond the classic biliary drainage can be performed that should be combined in an optimal manner. It is important for the endoscopist to know the individual situation of the patient to offer the most efficient minimal invasive relief in an optimal sequence and with the fewest number of sessions possible. Guiding principles are stated in Table 79.2.

Table 79.2 Timing of endoscopic interventions

– EUS before ERCP	EUS procedures are usually performed before ductal drainage to avoid problems of visibility or dislocation from previously implanted stents. Information from EUS might also contribute to the choice of stent for ductal decompression
– ERCP before duodenal stenting – Consider EUS-BD after duodenal stenting of if papilla not accessible	Definitive biliary drainage via ERCP should be ensured before duodenal stenting if the papilla is accessible. Transpapillary interventions are more complex and risky to perform with a duodenal SEMS placed and in these cases EUS-BD provides an effective alternative [53, 54]
– EUS celiac plexus block in same session with drainage procedure	Evaluate pain status before endoscopic interventions and possibly combine the drainage procedure with analgesic procedure
– Wait before manipulating on a EUS guided fistula	If possible, wait for 2–4 weeks before manipulation or consider stent fixation

79.8 Conclusion

Patients under palliation of pancreatic cancer today have the chance to live longer than ever possibly causing them to see secondary complications and creating a need for longer term palliation strategies. Endoscopic palliation in pancreatic cancer patients has developed from pure biliary drainage via ERCP with a plastic stent into a field of different interventions to choose from, especially due to the recent development of EUS guided interventions. Over time we hope to see more established concepts being challenged by less invasive endoscopic alternatives, such as in the case of PTCD or surgical gastro-enterostomy. With increasing options, the right choice, and sequence of the interventions gains importance in individually tailored concepts and rescue strategies.

References

1. Ducreux M, Seufferlein T, Van Laethem JL, Laurent-Puig P, Smolenschi C, Malka D, et al. Systemic treatment of pancreatic cancer revisited. Semin Oncol. 2019;46(1):28–38.
2. Yachimski PS, Ross A. The future of endoscopic retrograde cholangiopancreatography. Gastroenterology. 2017;153(2):338–44.
3. Dumonceau JM, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, et al. Endoscopic biliary stenting: indications, choice of stents, and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline – updated October 2017. Endoscopy. 2018;50(9):910–30.
4. Glomsaker T, Hoff G, Kvaloy JT, Soreide K, Aabakken L, Soreide JA. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. Br J Surg. 2013;100(3):373–80.
5. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc. 2009;70(1):80–8.
6. Eloubeidi MA, Decker GA, Chandrasekhara V, Chathadi KV, Early DS, Evans JA, et al. The role of endoscopy in the evaluation and management of patients with solid pancreatic neoplasia. Gastrointest Endosc. 2016;83(1):17–28.
7. Daroczi T, Bor R, Fabian A, Szabo E, Farkas K, Balint A, et al. Cost-effectiveness trial of self-expandable metal stents and plastic biliary stents in malignant biliary obstruction. Orv Hetil. 2016;157(7):268–74.
8. Martinez JM, Anene A, Bentley TG, Cangelosi MJ, Meckley LM, Ortendahl JD, et al. Cost effectiveness of metal stents in relieving obstructive jaundice in patients with pancreatic cancer. J Gastrointest Cancer. 2017;48(1):58–65.
9. Springfeld C, Jager D, Buchler MW, Strobel O, Hackert T, Palmer DH, et al. Chemotherapy for pancreatic cancer. Presse Med. 2019;48(3 Pt 2):e159–74.
10. Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57(2):178–82.
11. Wang AY. Is plastic stenting for pancreatic cancer still relevant or obsolete in 2015? Gastrointest Endosc. 2015;81(2):367–9.
12. Yoon WJ, Lee JK, Lee KH, Lee WJ, Ryu JK, Kim YT, et al. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc. 2006;63(7):996–1000.

13. Li J, Li T, Sun P, Yu Q, Wang K, Chang W, et al. Covered versus uncovered self-expandable metal stents for managing malignant distal biliary obstruction: a meta-analysis. PLoS One. 2016;11(2):e0149066.
14. Yang MJ, Kim JH, Yoo BM, Hwang JC, Yoo JH, Lee KS, et al. Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: a randomized controlled trial. Scand J Gastroenterol. 2015;50(12):1490–9.
15. Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11(1):27–37.
16. Sogabe Y, Kodama Y, Honjo H, Aoyama I, Muramoto Y, Koga E, et al. Tumor invasion to the arteries feeding the gallbladder as a novel risk factor for cholecystitis after metallic stent placement in distal malignant biliary obstruction. Dig Endosc. 2018;30(3):380–7.
17. Shimizu S, Naitoh I, Nakazawa T, Hayashi K, Miyabe K, Kondo H, et al. Predictive factors for pancreatitis and cholecystitis in endoscopic covered metal stenting for distal malignant biliary obstruction. J Gastroenterol Hepatol. 2013;28(1):68–72.
18. Wolfson D, Barkin JS, Chari ST, Clain JE, Bell RH Jr, Alexakis N, et al. Management of pancreatic masses. Pancreas. 2005;31(3):203–17.
19. Tan DM, Lillemoe KD, Fogel EL. A new technique for endoscopic removal of uncovered biliary self-expandable metal stents: stent-in-stent technique with a fully covered biliary stent. Gastrointest Endosc. 2012;75(4):923–5.
20. Bernon M, Kloppers C, Lindemann J, Krige JEJ, Jonas E. Recalcitrant embedded biliary self-expanding metal stents: a novel technique for endoscopic extraction. VideoGIE. 2019;4(2):72–5.
21. Vienne A, Hobeika E, Gouya H, Lapidus N, Fritsch J, Choury AD, et al. Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. Gastrointest Endosc. 2010;72(4):728–35.
22. Bulajic M, Panic N, Radunovic M, Scepanovic R, Perunovic R, Stevanovic P, et al. Clinical outcome in patients with hilar malignant strictures type II Bismuth-Corlette treated by minimally invasive unilateral versus bilateral endoscopic biliary drainage. Hepatobiliary Pancreat Dis Int. 2012;11(2):209–14.
23. Moole H, Dharmapuri S, Duvvuri A, Dharmapuri S, Boddireddy R, Moole V, et al. Endoscopic versus percutaneous biliary drainage in palliation of advanced malignant hilar obstruction: a meta-analysis and systematic review. Can J Gastroenterol Hepatol. 2016;2016:4726078.
24. Choi JH, Lee SH, You MS, Shin BS, Choi YH, Kang J, et al. Step-wise endoscopic approach to palliative bilateral biliary drainage for unresectable advanced malignant hilar obstruction. Sci Rep. 2019;9(1):13207.
25. Ge PS, Hamerski CM, Watson RR, Komanduri S, Cinnor BB, Bidari K, et al. Plastic biliary stent patency in patients with locally advanced pancreatic adenocarcinoma receiving downstaging chemotherapy. Gastrointest Endosc. 2015;81(2):360–6.
26. Rathmayer M, Heinlein W, Reiss C, Albert JG, Akoglu B, Braun M, et al. Cost assessment for endoscopic procedures in the German diagnosis-related-group (DRG) system – 5 year cost data analysis of the German Society of Gastroenterology project. Z Gastroenterol. 2017;55(10):1038–51.
27. Walter D, van Boeckel PG, Groenen MJ, Weusten BL, Witteman BJ, Tan G, et al. Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial. Gastroenterology. 2015;149(1):130–8.
28. Lamarca A, Rigby C, McNamara MG, Hubner RA, Valle JW. Impact of biliary stent-related events in patients diagnosed with advanced pancreatobiliary tumours receiving palliative chemotherapy. World J Gastroenterol. 2016;22(26):6065–75.
29. Wadsworth CA, Westaby D, Khan SA. Endoscopic radiofrequency ablation for cholangiocarcinoma. Curr Opin Gastroenterol. 2013;29(3):305–11.
30. Wang K, Zhu J, Xing L, Wang Y, Jin Z, Li Z. Assessment of efficacy and safety of EUS-guided biliary drainage: a systematic review. Gastrointest Endosc. 2016;83(6):1218–27.

31. Oh D, Park DH, Song TJ, Lee SS, Seo DW, Lee SK, et al. Optimal biliary access point and learning curve for endoscopic ultrasound-guided hepaticogastrostomy with transmural stenting. Ther Adv Gastroenterol. 2017;10(1):42–53.
32. Poincloux L, Rouquette O, Buc E, Privat J, Pezet D, Dapoigny M, et al. Endoscopic ultrasound-guided biliary drainage after failed ERCP: cumulative experience of 101 procedures at a single center. Endoscopy. 2015;47(9):794–801.
33. Bishay K, Boyne D, Yaghoobi M, Khashab MA, Shorr R, Ichkhanian Y, et al. Endoscopic ultrasound-guided transmural approach versus ERCP-guided transpapillary approach for primary decompression of malignant biliary obstruction: a meta-analysis. Endoscopy. 2019;51(10):950–60.
34. Ardengh JC, Lopes CV, Kemp R, Dos Santos JS. Different options of endosonography-guided biliary drainage after endoscopic retrograde cholangio-pancreatography failure. World J Gastrointest Endosc. 2018;10(5):99–108.
35. Uemura S, Iwashita T, Iwata K, Mukai T, Osada S, Sekino T, et al. Endoscopic duodenal stent versus surgical gastrojejunostomy for gastric outlet obstruction in patients with advanced pancreatic cancer. Pancreatology. 2018; https://doi.org/10.1016/j.pan.2018.04.015.
36. Stier MW, Waxman I. Lumen-apposing metal stents: which one and why? Gastrointest Endosc Clin N Am. 2018;28(2):207–17.
37. Ogura T, Higuchi K. Technical tips for endoscopic ultrasound-guided hepaticogastrostomy. World J Gastroenterol. 2016;22(15):3945–51.
38. Shah SL, Perez-Miranda M, Kahaleh M, Tyberg A. Updates in therapeutic endoscopic ultrasonography. J Clin Gastroenterol. 2018;52(9):765–72.
39. Cho DH, Lee SS, Oh D, Song TJ, Park DH, Seo DW, et al. Long-term outcomes of a newly developed hybrid metal stent for EUS-guided biliary drainage (with videos). Gastrointest Endosc. 2017;85(5):1067–75.
40. De Cassan C, Bories E, Pesenti C, Caillol F, Godat S, Ratone JP, et al. Use of partially covered and uncovered metallic prosthesis for endoscopic ultrasound-guided hepaticogastrostomy: results of a retrospective monocentric study. Endosc Ultrasound. 2017;6(5):329–35.
41. Park JK, Woo YS, Noh DH, Yang JI, Bae SY, Yun HS, et al. Efficacy of EUS-guided and ERCP-guided biliary drainage for malignant biliary obstruction: prospective randomized controlled study. Gastrointest Endosc. 2018;88(2):277–82.
42. Costamagna G, Gabbrielli A, Mutignani M, Perri V, Crucitti F. Treatment of "obstructive" pain by endoscopic drainage in patients with pancreatic head carcinoma. Gastrointest Endosc. 1993;39(6):774–7.
43. Tham TC, Lichtenstein DR, Vandervoort J, Wong RC, Slivka A, Banks PA, et al. Pancreatic duct stents for "obstructive type" pain in pancreatic malignancy. Am J Gastroenterol. 2000;95(4):956–60.
44. Costamagna G, Mutignani M. Pancreatic stenting for malignant ductal obstruction. Dig Liver Dis. 2004;36(9):635–8.
45. Wehrmann T, Riphaus A, Frenz MB, Martchenko K, Stergiou N. Endoscopic pancreatic duct stenting for relief of pancreatic cancer pain. Eur J Gastroenterol Hepatol. 2005;17(12):1395–400.
46. Fasanella KE, Davis B, Lyons J, Chen Z, Lee KK, Slivka A, et al. Pain in chronic pancreatitis and pancreatic cancer. Gastroenterol Clin N Am. 2007;36(2):335–64. ix
47. Ceyhan GO, Demir IE, Rauch U, Bergmann F, Muller MW, Buchler MW, et al. Pancreatic neuropathy results in "neural remodeling" and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer. Am J Gastroenterol. 2009;104(10):2555–65.
48. Dawod E, Kahaleh M. Management of benign and malignant pancreatic duct strictures. Clin Endosc. 2018;51(2):156–60.
49. Kamata K, Takenaka M, Minaga K, Sakurai T, Watanabe T, Nishida N, et al. EUS-guided pancreatic duct drainage for repeat pancreatitis in a patient with pancreatic cancer. Oncology. 2017;93(Suppl 1):87–8.
50. Singh SM, Longmire WP Jr, Reber HA. Surgical palliation for pancreatic cancer. The UCLA experience. Ann Surg. 1990;212(2):132–9.

51. Tsauo J, Yoo MW, Song HY, Hwang DW, Park JH, Ryu MH, et al. Partially-covered stent placement versus surgical gastrojejunostomy for the palliation of malignant gastroduodenal obstruction secondary to pancreatic cancer. Abdom Radiol (NY). 2016;41(11):2233–40.
52. Yoshida Y, Fukutomi A, Tanaka M, Sugiura T, Kawata N, Kawai S, et al. Gastrojejunostomy versus duodenal stent placement for gastric outlet obstruction in patients with unresectable pancreatic cancer. Pancreatology. 2017;17(6):983–9.
53. Yamao K, Kitano M, Takenaka M, Minaga K, Sakurai T, Watanabe T, et al. Outcomes of endoscopic biliary drainage in pancreatic cancer patients with an indwelling gastroduodenal stent: a multicenter cohort study in West Japan. Gastrointest Endosc. 2018;88(1):66–75.
54. Staub J, Siddiqui A, Taylor LJ, Loren D, Kowalski T, Adler DG. ERCP performed through previously placed duodenal stents: a multicenter retrospective study of outcomes and adverse events. Gastrointest Endosc. 2018;87(6):1499–504.
55. Rimbas M, Larghi A, Costamagna G. Endoscopic ultrasound-guided gastroenterostomy: are we ready for prime time? Endosc Ultrasound. 2017;6(4):235–40.
56. Itoi T, Baron TH, Khashab MA, Tsuchiya T, Irani S, Dhir V, et al. Technical review of endoscopic ultrasonography-guided gastroenterostomy in 2017. Dig Endosc. 2017;29(4):495–502.
57. Perez-Miranda M, Tyberg A, Poletto D, Toscano E, Gaidhane M, Desai AP, et al. EUS-guided gastrojejunostomy versus laparoscopic gastrojejunostomy: an international collaborative study. J Clin Gastroenterol. 2017;51(10):896–9.
58. Khashab MA, Bukhari M, Baron TH, Nieto J, El Zein M, Chen YI, et al. International multicenter comparative trial of endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for the treatment of malignant gastric outlet obstruction. Endosc Int Open. 2017;5(4):E275–81.
59. Krafft MR, Hsueh W, James TW, Runge TM, Baron TH, Khashab MA, et al. The EDGI new take on EDGE: EUS-directed transgastric intervention (EDGI), other than ERCP, for Roux-en-Y gastric bypass anatomy: a multicenter study. Endosc Int Open. 2019;7(10):E1231–40.
60. Kedia P, Tyberg A, Kumta NA, Gaidhane M, Karia K, Sharaiha RZ, et al. EUS-directed transgastric ERCP for Roux-en-Y gastric bypass anatomy: a minimally invasive approach. Gastrointest Endosc. 2015;82(3):560–5.
61. Wang BC, Furnback W. Modelling the long-term outcomes of bariatric surgery: a review of cost-effectiveness studies. Best Pract Res Clin Gastroenterol. 2013;27(6):987–95.
62. Kedia P, Tarnasky PR, Nieto J, Steele SL, Siddiqui A, Xu MM, et al. EUS-directed transgastric ERCP (EDGE) versus laparoscopy-assisted ERCP (LA-ERCP) for Roux-en-Y gastric bypass (RYGB) anatomy: a multicenter early comparative experience of clinical outcomes. J Clin Gastroenterol. 2019;53(4):304–8.
63. Irani S, Yang J, Khashab MA. Mitigating lumen-apposing metal stent dislodgment and allowing safe, single-stage EUS-directed transgastric ERCP. VideoGIE. 2018;3(10):322–4.
64. Yasuda I, Wang HP. Endoscopic ultrasound-guided celiac plexus block and neurolysis. Dig Endosc. 2017;29(4):455–62.
65. Michaels AJ, Draganov PV. Endoscopic ultrasonography guided celiac plexus neurolysis and celiac plexus block in the management of pain due to pancreatic cancer and chronic pancreatitis. World J Gastroenterol. 2007;13(26):3575–80.
66. Bang JY, Sutton B, Hawes RH, Varadarajulu S. EUS-guided celiac ganglion radiofrequency ablation versus celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial (with videos). Gastrointest Endosc. 2019;89(1):58–66.
67. Han J, Chang KJ. Endoscopic ultrasound-guided direct intervention for solid pancreatic tumors. Clin Endosc. 2017;50(2):126–37.

Chapter 80
Surgical Palliation for Inoperable Pancreatic Cancer

Svein Olav Bratlie and Kjetil Søreide

Take Home Messages

- Biopsies should be secured for histopathological verification of the cancer in the case of metastatic or irresectable disease found at laparotomy.
- Self-expandable metallic stent is first-line treatment for biliary obstruction, a surgical bypass may be considered only in highly selected patients.
- A gastrojejunostomy (open or laparoscopically) is a viable option for gastroduodenal outlet obstruction in the palliative setting.
- A "wait-and-see" strategy with biliary- and/or enteric stent on demand should be the ruling attitude for patients that may be considered for reevaluation and eventually a second future surgical attempt.

Pearls and Pitfalls

- Patients with an estimated short lifespan (<4 months) are poor candidates for surgical palliation and less invasive alternatives should be preferred.
- Most palliative interventions for biliary obstruction, gastroduodenal obstruction or intractable pain can be managed by non-operative means as first choice.
- Complications from surgical palliation may delay or even prevent patients from going to palliative chemotherapy.

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Future Perspectives

- Most studies done in the palliative setting are out dated and better data including patient-preferences and quality of life are needed.
- With the increasing population of elderly, frail and inoperable patients with pancreatic cancer, specific studies to look at palliative strategies are needed.
- Increasing use of neoadjuvant therapy in locally advanced (and oligometastatic) disease may warrant investigation into optimal strategies for obstructive relief, considering potential for conversion to resection after treatment.

80.1 Introduction

Although the annual incidence of pancreatic cancer is relatively low, the cancer related mortality is high. At diagnosis, more than 80% of the patients are beyond the stage of the possibility of treatment with curative intent. With novel and more effective chemotherapy regimens (e.g. FOLFIRINOX), a proportion of patients with locally advanced disease are currently considered for neoadjuvant induction or conversion therapy [1]. However, in consideration of an intended R2 resection or debulking procedure as part of palliative care, the available data suggests it is to be avoided, due to the associated morbidity and mortality [2–4].

Patients with pancreatic- and periampullary cancer are scheduled for surgery with curative intent after a multidisciplinary evaluation based on imaging, performance-status, comorbidity, and with patient's informed consent. The clinical preoperative assessment includes symptom evaluation regarding jaundice due to biliary obstruction, malnutrition due to gastric or duodenal outlet obstruction and pain. At time of surgery, approximately 10% of the patients present with metastatic spread (liver or peritoneum) or locally advanced, irresectable disease [5]. At this point, the surgeon needs to take into account the abovementioned symptoms as well as relating the current findings coupled to the future life-expectancy for the patient on the table, first and foremost in aspect of quality of life. The surgeon may select from surgical palliative by-pass procedure or, chose a minimally invasive endoscopic approach. A third option would be to close the abdomen without any further intervention ("wait and see").

Notably, several options have been developed in endoscopic and ultrasound-guided techniques over the recent years, which offers minimal-invasive and effective treatments to most patients [6–9]. Thus, endoscopic options remain the first choice in most patients. Endoscopic and minimal-invasive alternatives are discussed in other chapters of the book. Hence, this chapter will focus on surgical options and, where available, comparative data between the surgical and alternative options on patient outcomes.

80.2 Decision Making

The unexpected discovery of metastatic spread or locally advanced pancreatic- or periampulary cancer at surgery with curative intent puts the surgeon into a challenging situation in deciding what to do next. Alternative plans should be

discussed with the patient in the preoperative setting of consent. Although the preoperative assessment and the perioperative findings are considered and the surgeon can find a certain level of evidence-based recommendations in the available literature, eventually an individualised palliative strategy is needed for each patient. For patients diagnosed with unexpected metastatic/locally advanced disease in theatre, one should take into account that these patients are selected from the start, that is, regarded as physically fit to undergo a planned resection. From that perspective, these patients may be in a relatively good performance status and with limited comorbidity. Therefore, the subsequent plans for palliative oncological treatment must be kept in mind and biopsies for histopathological verification of the cancer must be secured.

80.3 The Unaffected Patient

Patients with cancer in the tail of the pancreas often present with sparse or no cancer-related symptoms. Metastatic spread at surgery may often be left without any further intervention. Bulky tumours, with their proximity to the stomach, may eventually affect the patient's nutritional status by development of nausea or mechanical compression, but there is no support for prophylactic palliative surgical resection in these patients. The remaining life-expectancy is short for patients with metastatic spread of caudal pancreatic cancer [10, 11].

In the case of metastatic spread detected at surgery for cancer in the body of the pancreas, the proximity to the nerve plexus at the coeliac trunk may indicate the need for prophylactic neurolytic celiac plexus block in an attempt to avoid future pain [12].

Patients with the tumour located in the head of the pancreas (or periampullary) may either be unaffected due to prior stenting of the biliary tract or, suffer from a tumour not affecting the biliary tract or enteric lumen. When metastatic spread or irresectable disease is discovered at surgery, the surgeon needs to evaluate the future risk of obstructive symptoms.

Two randomized controlled trials performed two decades ago, found that prophylactic single or double bypass was superior to endoscopic stenting regarding long-term patency for biliary and gastric outlet obstruction in the palliative setting [13, 14]. The short-term benefits of stenting were early oral intake and shorter hospital stay compared to bypass surgery. However, in the long run, the surgical bypass group had fewer readmissions due to obstruction. There were no differences in survival between the groups. These are the only two trials referred to in a later Cochrane systematic review performed 2013 [15]. The SUSTENT study published in 2010 compared bypass surgery and stent for malignant gastric outlet obstruction, finding long-term benefit for the surgery group regarding reinterventions [16].

Taken together, these research groups recommend bypass surgery for patients with a long life-expectancy (at least >4–6 months) and, leaving palliative stenting for patients with an expected lifespan of less than 2 months. In a subsequent meta-analysis of both randomized and non-randomized trials, the survival outcomes

where similar for stent and surgical bypass. However, the short-term outcomes favoured stents, with shorter time to oral intake, fewer complications and shorter hospital stay [17]. Of note, none of the data report on overall medical effects, costs and patients reported quality of life.

In the last decade, patient selection for surgery with curative intent is based on improved preoperative assessment by more accurate and improved imaging. The oncological treatment options have developed with improved impact on survival, even in the palliative setting [18, 19]. Hence, the selected group of patients found to have metastatic spread or irresectable disease at time of surgery are currently more likely to present with a fairly good performance-status with a suspected survival of more than 4 months.

Based on the recommendations in the abovementioned Cochrane review, almost all of these patients would benefit from a by-pass procedure. However, more recent trials including quality of life and health economics speak in favour of the less invasive stent strategy [5, 20]. The fast return to oral intake and early home-admission is weighted higher than the risk of readmission to hospital [21]. The previous practice of prophylactic biliodigestive shunt in the palliative setting has now been replaced by the "wait and see" strategy with endoscopic stent "on demand" [5, 22, 23].

If the patient preoperatively has no jaundice (no obstruction or stented) and without signs of ongoing enteric obstruction, the surgeon should close the abdomen without further intervention when metastatic spread or irresectable disease is found at exploration. Patients that prior to surgery were treated with a biliary plastic stent might benefit from changing the stent to a semi-covered metallic stent for superior patency and cost effectiveness [24].

80.3.1 Biliary Tract Obstruction

If no severe symptoms due to longstanding jaundice, the unaffected patients may proceed to surgery with curative intent without prior biliary drainage [25, 26]. On the other hand, the symptomatic jaundiced patients most often are provided with a biliary plastic or metal stent during preoperative assessment in order to improve nutritional- and performance-status (WHO/ECOG) prior to surgery [27]. In jaundiced patients with borderline or locally advanced disease referred for neoadjuvant chemotherapy, the biliary stenting is mandatory prior to commencement of chemotherapy in order to decrease serum-bilirubin levels.

If unexpected metastatic spread or irresectable disease is found at surgery the surgeon needs to consider which intervention that is best suited for the patient. As mentioned earlier, the well-drained (with metal stent) patient may be left without further intervention. On the other hand, the undrained patient would need a biliary diversion. The laparotomy is already performed, and in this situation it is a well-established practice to then proceed with the choledoco- or hepatico-jejunostomy with favourable long-term patency [15]. However, in several centres a hybrid intervention with perioperative endoscopic biliary stenting is performed, either during laparotomy or immediately after wound closure. Speaking in favour of this strategy

is the less invasive impact and lower risk of complications from the surgery, earlier start of oral intake and shorter hospital stay, better quality of life, and possibly even shorter time to pass before start of palliative oncological treatment [28].

80.3.2 Surgical Biliary Diversion

The surgical biliary diversion is preferably constructed as a choledocho- or hepatico-jejunostomy. If metastatic spread of the disease is detected at laparotomy, a strategy of less-is-more may be at hand. Leaving the gallbladder in place, a limited dissection to identify the anterior part of the choledochal duct is performed. After a longitudinal incision in the duct, a side-to-side choledocho-jejunostomy is constructed, the proximal jejunum mobilised antecolically. On the other hand, if the dissection during laparotomy has proceeded through cholecystectomy, and the exploration of the hepato-duodenal ligament is performed before cessation due to irresectable disease, an end-to-side hepatico-jejunostomy is constructed (Fig. 80.1). Because of the proximity to the primary tumor, and the risk of future tumor overgrowth of the cystic duct, a cholecysto-enterostomy should be considered only in highly selected patients with short life-expectancy. Due to the future risk of duodenal outlet obstruction, a choledocho-duodenostomy is not preferred as a first-line solution for palliative biliary diversion.

In the end, there is no high-level evidence on which biliary diversion to perform. The individual surgical judgement in each case is to be performed, based on patient-related aspects on life-expectancy and quality of remaining life [29]. Although based on old trials, the highest level of evidence recommendations are surgical biliary diversion in patients with good performance status and long life expectancy [15].

In a meta-analysis, the durability of surgical bypass for biliary obstruction was found to be longer [30] with fewer subsequent hospitalizations compared to stent. However, no statistically significant differences in success rates between the two treatments (risk ratio [RR] 0.99; 95% CI 0.93–1.05; P = 0.67) was found, nor any difference in major complications and mortality from surgical bypass (RR 1.54; 95% CI 0.87–2.71; P = 0.14) [30]. Recurrent biliary obstruction was significantly less frequent after surgical bypass than after stent placement (RR 0.14; 95% CI 0.03–0.63; P < 0.01). Despite similar overall survival rates, longer survival was associated with more hospital days before death in stent patients than in surgical patients [30].

80.3.3 Palliation for Gastric or Duodenal Outlet Obstruction

Pancreatic- and periampullary cancer may cause gastric- or duodenal outlet obstruction. Nausea, vomiting, malnutrition and cachexia are disabling symptoms with an enormous impact on quality of life, and in the end an impact on life expectancy. Intervention is paramount, and the patient assessed to primary cancer resection is

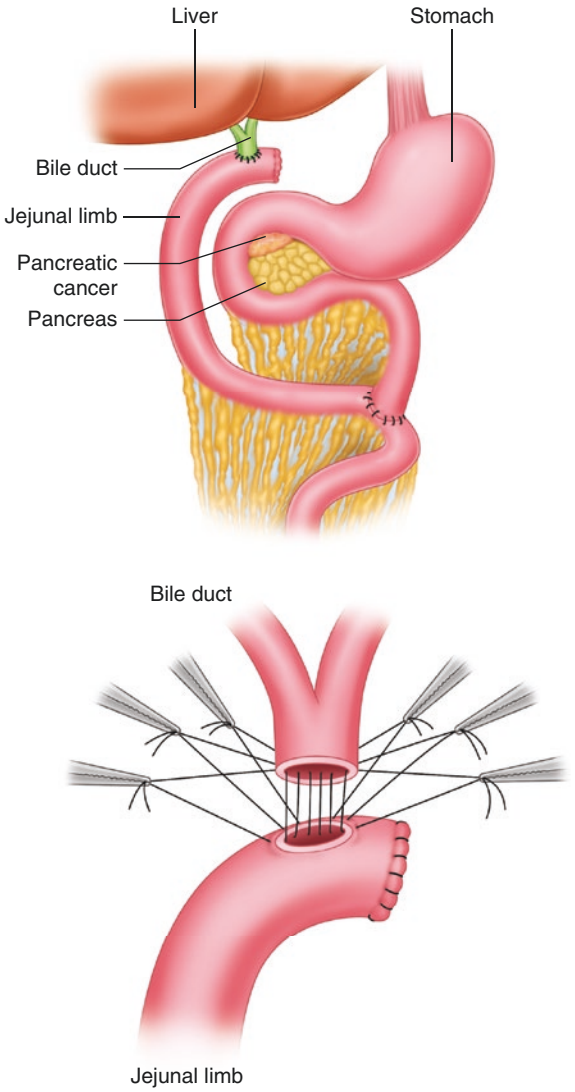


Fig. 80.1 Hepaticojejunostomy (end-to-side anastomosis). An end-to-side anastomosis by interrupted or continuous layer sutures. The bile duct is usually wide due to the ongoing biliary obstruction

prioritized for surgery among fellow patients. In selected cases, i.e. if neoadjuvant chemotherapy has been indicated, patients may have received an enteric stent prior to surgery.

The unexpected metastatic spread or irresectable disease at surgery may indicate the inevitable need of a gastric diversion. To perform a gastrojejunostomy is well established practice with good long-term patency, and in the setting with simultaneous undrained biliary obstruction, a "double bypass" with concomitant hepaticojejunostomy may be performed [15, 16, 31].

If the biliary tract is without obstruction at laparotomy, or preoperatively well drained (metal stent), a single bypass is sufficient, excluding the risk of

complications from a prophylactically performed hepaticojejunostomy. If an endoscopically depleted enteric stent is already in place, the first line treatment for gastric or duodenal outlet obstruction would be to close the abdomen without further intervention, referring to limited complication risk, early oral intake, and shorter hospital stay, and inevitably receive palliative or attempt at conversion chemotherapy [22].

80.3.4 Surgical Enteric Diversion

The surgical enteric diversion to relive the patient from gastric- or duodenal outlet obstruction is constructed by performing a side-to-side gastrojejunostomy. The anastomosis is preferably placed at the posterior side of the antrum or corpus of the stomach by using a stapling device. The proximal jejunum is mobilised and placed in an antecolic fashion to the posterior side of the major curvature of the stomach, if possible. In case of a bulky tumor, the surgeon may choose to place the anastomosis at the anterior side of the stomach (Fig. 80.2).

80.3.5 Double By-Pass

In the case of biliary- and enteric obstruction, a double by-pass is constructed by mobilising the proximal jejunum antecolically towards the posterior side of the antrum or corpus of the stomach. A stapled side-to-side anastomosis is performed. The jejunum is then divided by a stapler about 30–40 cm downstream of the gastrojejunostomy. A "Roux-en-Y" loop is then constructed, performing a hand-sewn end-to-side hepaticojejunostomy. Finally, 30–40 cm downstream, the stapled enteroentero-anastomosis is performed (Fig. 80.3).

80.3.6 Neurolytic Celiac Plexus Block

In patients with a history of pain preoperatively, often treated with high doses of oral opioids, a perioperative neurolytic celiac plexus block may be performed. This may even be indicated prophylactically if perioperative findings of an irresectable tumor includes infestation of the coeliac trunc. At laparotomy, an injection of 50% alcohol, 20 cc on either side of the aorta at the level of the celiac trunc is performed [32] (Fig. 80.4). In a randomized placebo-controlled trial, Wong et al. could present improved long lasting analgesia in the group receiving neurolytic plexus block versus the opioid-only-group. There were no difference in quality of life or survival [12]. Further, a Cochrane database systematic review concluded that neurolytic celiac plexus block significantly reduses the opioid consumption among patients in the palliative setting [33]. The European Palliative Care Reasearch Collaborative concludes the superior analgetic efficacy of neurolytic celiac plexus block in

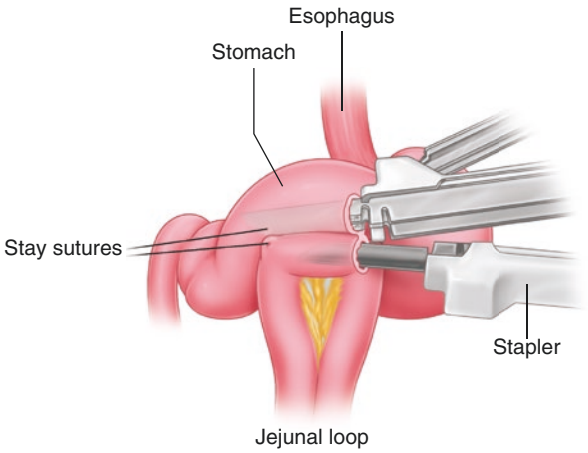
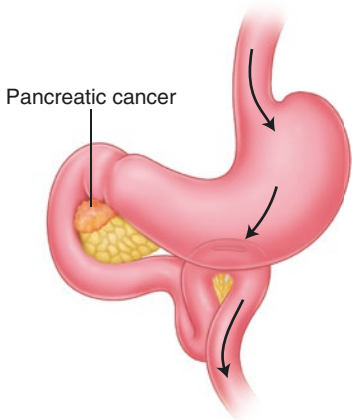


Fig. 80.2 Gastrojejunostomy. A side-to-side anastomosis using a stapler to facilitate gastroenteric continuity. The jejunal loop is brought up antecolic and o preferably placed on the posterior side of the stomach, but in case of tumor masses or peritoneal carcinomatosis it may also be placed on the anterior side. The procedure may also be entertained by laparoscopic access



pancreatic cancer patients, in their review regarded as high level of evidence [34]. This intervention can now be entertained via several routes of access, including percutaneously, endoscopic (EUS-guided) or operatively either as a laparoscopic or open procedure [12, 35–42]. However, surgical intervention under general anaesthesia should only be reserved for otherwise fit patients with an expected long-term survival when less invasive methods have failed to achieve proper pain control. Also, laparoscopic celiac plexus block may be entertained as part of laparoscopic exploration, when irresectable disease (e.g. peritoneal carcinomatosis) have been found.

80.4 Surgery at the End of Life

For patientd with extensive disease, high metastatic disease load or extensive peritoneal metastasis for when the expected reminaing life-time is short, surgical intervention is to be avoided. In such patients, one should carefully discuss the patients symptom burden and wishes together with the multidisciplinary (preferably

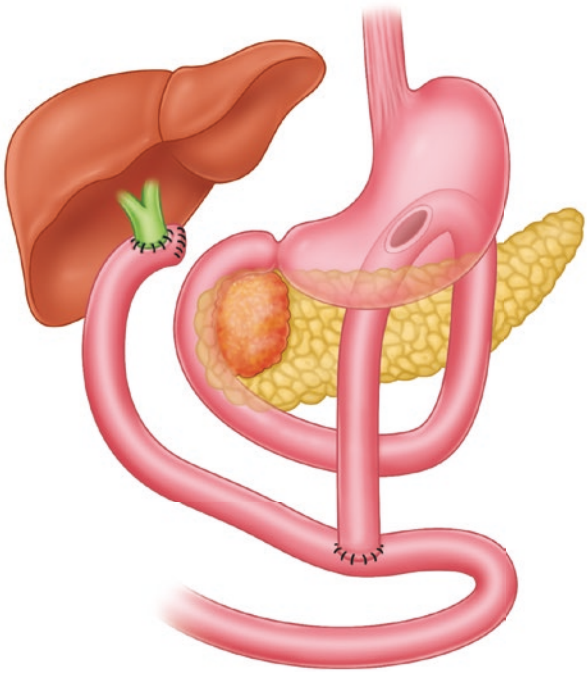


Fig. 80.3 Double bypass. A hepato-jejunostomy and a gastro-jejunostomy in a Roux-en-Y construction

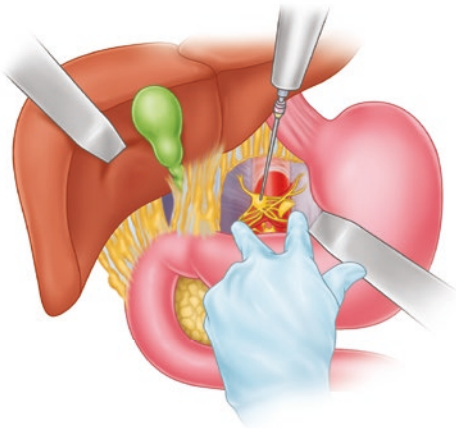


Fig. 80.4 Celiac plexus block. Chemical splancnicectomy by injecting 20 cc of 50% alcohol on each side of the aorta at the level of the coeliac trunk

palliative) team and family members, with consideration of the least invasive approach to alleviate symptoms. One needs to consider the risk of increased morbidity and also mortality even with endoscopic procedures in this setting, as elderly patients with comorbidty and malignacy is the group at highest risk of death after ERCP [43]. Although less optimal, one may consider percutaneos drainage procedures for biliary obstruction.

If endoscopic stenting is not feasible, a percutaneous endoscopic gastrostomy (PEG) may be sufficient to aleviate gastroduodenal outlet obstruction. Surgical intervention in the most frail patients at the end of the disease course is often associated with deterimental outcome and even mortality.

Pain is a very common symptom in pancreatic cancer, and can sometimes be disabling and diffiult to manage. Population based studies suggest there currently exist an undertreatment in patients with pain caused by unresected pancreatic cancer [44]. While opioids and step up medical management can be sufiiccient for many patient with pain, one should consider interventional options as additions to optimize pain management. Data suggest that use of celiac plexus blockage is associated with improvement in pain control, lower doses of opioids and hence reduced side-effects from opioids [33, 38].

80.5 Future Perspective

For now, current practice is to treat pancreatic ductal adenocarcinoma with metastatic spread as an incurable disease, and a treatment with curative intent is converted into a palliative strategy.

However, the last decade the oncologic combination-therapies are improving, and a number of highly selected patients with oligometastatic disease may in the future be candidates for oncologic conversion therapy and re-evaluated for future surgery, again with curative intent. Hopefully, even future immunotherapy may change our attitude to metastatic disease.

Moreover, during the last decade the definition of irresectable disease has been challenged. Surgeons now consider vascular resection (portal- and superior mesenteric vein) as feasible in selected patients. Further, in highly specialised centres, borderline resectable and locally advanced pancreatic cancers are now considered for surgical attempt (including arterial resection) aiming at radical resection (R0) after oncologic induction or conversion therapy.

Taken together, oligometastatic and locally advanced pancreatic cancer discovered at laparotomy may in the near future be considered for treatment with curative intent. Therefore, a “wait-and-see” strategy, with biliary and enteric stent on demand should be an appealing attitude when the surgeon has found the unexpected metastatic or irresectable disease at laparotomy, deciding what to do next [45].

References

1. Hank T, Strobel O. Conversion surgery for advanced pancreatic cancer. J Clin Med. 2019;8:1945.
2. Gillen S, Schuster T, Friess H, Kleeff J. Palliative resections versus palliative bypass procedures in pancreatic cancer—a systematic review. Am J Surg. 2012;203:496–502.
3. Gurusamy KS, Kumar S, Davidson BR, Fusai G. Resection versus other treatments for locally advanced pancreatic cancer. Cochrane Database Syst Rev. 2014;(2):Cd010244.

4. Tol JA, Eshuis WJ, Besselink MG, van Gulik TM, Busch OR, Gouma DJ. Non-radical resection versus bypass procedure for pancreatic cancer – a consecutive series and systematic review. Eur J Surg Oncol. 2015;41:220–7.
5. Stark A, Hines OJ. Endoscopic and operative palliation strategies for pancreatic ductal adenocarcinoma. Semin Oncol. 2015;42:163–76.
6. Nabi Z, Reddy DN. Endoscopic palliation for biliary and pancreatic malignancies: recent advances. Clin Endosc. 2019;52:226–34.
7. Miller CS, Barkun AN, Martel M, Chen YI. Endoscopic ultrasound-guided biliary drainage for distal malignant obstruction: a systematic review and meta-analysis of randomized trials. Endosc Int Open. 2019;7:E1563–e73.
8. Hathorn KE, Bazarbashi AN, Sack JS, et al. EUS-guided biliary drainage is equivalent to ERCP for primary treatment of malignant distal biliary obstruction: a systematic review and meta-analysis. Endosc Int Open. 2019;7:E1432–e41.
9. Han SY, Kim SO, So H, Shin E, Kim DU, Park DH. EUS-guided biliary drainage versus ERCP for first-line palliation of malignant distal biliary obstruction: a systematic review and meta-analysis. Sci Rep. 2019;9:16551.
10. Tomasello G, Ghidini M, Costanzo A, et al. Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies. J Gastrointest Oncol. 2019;10:259–69.
11. van Erning FN, Mackay TM, van der Geest LGM, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol. 2018;57:1655–62.
12. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA. 2004;291:1092–9.
13. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg. 1999;230:322–8; discussion 8–30.
14. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. Ann Surg. 2003;238:894–902; discussion −5.
15. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. Cochrane Database Syst Rev. 2013;(10):CD008533.
16. Jeurnink SM, Steyerberg EW, van Hooft JE, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71:490–9.
17. Nagaraja V, Eslick GD, Cox MR. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction-a systematic review and meta-analysis of randomized and non-randomized trials. J Gastrointest Oncol. 2014;5:92–8.
18. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31:23–9.
19. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
20. Jeurnink SM, Polinder S, Steyerberg EW, Kuipers EJ, Siersema PD. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. J Gastroenterol. 2010;45:537–43.
21. Chandrasegaram MD, Eslick GD, Mansfield CO, et al. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction. Surg Endosc. 2012;26:323–9.
22. Williamsson C, Wennerblom J, Tingstedt B, Jonsson C. A wait-and-see strategy with subsequent self-expanding metal stent on demand is superior to prophylactic bypass surgery for unresectable periampullary cancer. HPB (Oxford). 2016;18:107–12.
23. Kneuertz PJ, Cunningham SC, Cameron JL, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. J Gastrointest Surg. 2011;15:1917–27.

24. Walter D, van Boeckel PG, Groenen MJ, et al. Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial. Gastroenterology. 2015;149:130–8.
25. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362:129–37.
26. Lee PJ, Podugu A, Wu D, Lee AC, Stevens T, Windsor JA. Preoperative biliary drainage in resectable pancreatic cancer: a systematic review and network meta-analysis. HPB (Oxford). 2018;20:477–86.
27. Song TJ, Lee JH, Lee SS, et al. Metal versus plastic stents for drainage of malignant biliary obstruction before primary surgical resection. Gastrointest Endosc. 2016;84:814–21.
28. Angelico R, Khan S, Dasari B, et al. Is routine hepaticojejunostomy at the time of unplanned surgical bypass required in the era of self-expanding metal stents? HPB (Oxford). 2017;19:365–70.
29. Perinel J, Adham M. Palliative therapy in pancreatic cancer-palliative surgery. Transl Gastroenterol Hepatol. 2019;4:28.
30. Glazer ES, Hornbrook MC, Krouse RS. A meta-analysis of randomized trials: immediate stent placement vs. surgical bypass in the palliative management of malignant biliary obstruction. J Pain Symptom Manag. 2014;47:307–14.
31. Mintziras I, Miligkos M, Wachter S, Manoharan J, Bartsch DK. Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis. Surg Endosc. 2019;33:3153–64.
32. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg. 1993;217:447–55; discussion 56–7.
33. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev. 2011;(3):CD007519.
34. Mercadante S, Klepstad P, Kurita GP, Sjogren P, Giarratano A, European Palliative Care Research C. Sympathetic blocks for visceral cancer pain management: a systematic review and EAPC recommendations. Crit Rev Oncol Hematol. 2015;96:577–83.
35. Strong VE, Dalal KM, Malhotra VT, et al. Initial report of laparoscopic celiac plexus block for pain relief in patients with unresectable pancreatic cancer. J Am Coll Surg. 2006;203:129–31.
36. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007;102:430–8.
37. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. 2009;54:2330–7.
38. Nagels W, Pease N, Bekkering G, Cools F, Dobbels P. Celiac plexus neurolysis for abdominal cancer pain: a systematic review. Pain Med. 2013;14:1140–63.
39. Vayne-Bossert P, Afsharimani B, Good P, Gray P, Hardy J. Interventional options for the management of refractory cancer pain—what is the evidence? Support Care Cancer. 2016;24:1429–38.
40. Lu F, Dong J, Tang Y, et al. Bilateral vs. unilateral endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain management in patients with pancreatic malignancy: a systematic review and meta-analysis. Support Care Cancer. 2018;26:353–9.
41. Tepelenis K, Tsimogiannis KE, Zikos N, et al. Laparoscopic versus open approach to neurolytic celiac plexus block in inoperable pancreatic cancer. ANZ J Surg. 2018;88:E767–e71.
42. Lou S. Endoscopic ultrasound-guided celiac plexus neurolysis to alleviate intractable pain caused by advanced pancreatic cancer. Surg Laparosc Endosc Percutan Tech. 2019;29:472–5.
43. Glomsaker T, Hoff G, Kvaloy JT, Soreide K, Aabakken L, Soreide JA. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. Br J Surg. 2013;100:373–80.
44. Tung S, Coburn NG, Davis LE, et al. Population-based study of the prevalence and management of self-reported high pain scores in patients with non-resected pancreatic adenocarcinoma. Br J Surg. 2019;106:1666–75.
45. Brunner M, Wu Z, Krautz C, Pilarsky C, Grutzmann R, Weber GF. Current clinical strategies of pancreatic cancer treatment and open molecular questions. Int J Mol Sci. 2019;20:4543.

Chapter 81
Definitive or Palliative Radiotherapy for Unresectable Pancreatic Cancer

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Take Home Messages

- Multidisciplinary approach should be utilized
- Palliative care should be involved at the outset for symptom control
- Radiotherapy can be utilized for both simple palliation with standard external beam or with sophisticated technology that delivers high dose stereotactic treatment

Pearls and Pitfalls

- Assessing the patient's treatment journey in a compartmentalized rather than a holistic fashion
- Radiotherapy should be delivered in a fashion to improve the patient's quality of life
- Re-irradiation is safe and possible in patients who've had previous radiotherapy

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Future Perspectives
- Targeted therapy and immunotherapy may change the outcomes of locally advanced/metastatic pancreatic cancer
- Targeting oligometastatic disease with radiation may change outcomes
- MR-Linac is an evolving modality and will provide enhanced image guidance to target pancreatic tumors with radiotherapy

81.1 Introduction

At the initial presentation, 15–30% of pancreatic cancer patients have unresectable disease [1] and 50% of patients present with metastasis [2]. With multiple, severe symptoms, unresectable pancreatic cancer is a challenging entity to treat. Radiotherapy can play a role in management depending on local extent of disease, presence/absence of metastasis, treatment goals, patient's performance status and patient preference (Box 81.1).

Box 81.1 Definitions
Definitive radiotherapy provides durable local control for unresectable, non-metastatic pancreatic cancer [3].

Palliative radiotherapy can be used to alleviate symptoms that are caused by the primary tumor or metastatic deposits, with shrinkage of the tumor [4], interruption of nerve connections, and disruption of inflammatory mediators secreted by the tumor thought to play a role [5].

As the pancreas lies in close proximity to the duodenum, stomach, small bowel, and liver, it is important to be cognizant of these organs at risk when delivering radiotherapy so as to minimize acute and late toxicities (Box 81.2), respecting the concept of therapeutic ratio in radiotherapy [6]. There is a wide spectrum of approaches when it comes to treating a patient with unresectable pancreatic cancer with radiotherapy, ranging from supportive care to stereotactic body radiotherapy (Fig. 81.1). Supportive care is traditionally rendered if the patient is judged to have

Fig. 81.1 Spectrum of care offered to patients with unresectable/borderline resectable pancreatic cancer depending on performance status, prognosis and disease burden

a short prognosis and/or poor performance status that intervention would be futile. External beam radiotherapy with/without chemotherapy can be delivered in patients with performance status that allows them to endure the treatment. Stereotactic treatment can be delivered in patients with adequate performance status provided that the technology is available to do so.

Box 81.2 Definitions of Toxicity
Acute toxicities:
Nausea, vomiting, diarrhea, dermatitis, anorexia, weight loss and fatigue.
Late toxicities:
Small bowel obstruction, Small bowel perforation, Biliary stenosis and radiation induced malignancies.

The purpose of this chapter is to discuss the role of definitive radiotherapy in the setting of locally advanced/unresectable pancreatic cancer and to describe the symptom alleviating effects of palliative radiotherapy for patients with pancreatic cancer who have no avenues for curative therapy.

81.2 Definitive Radiotherapy for Locally Advanced/ Unresectable Pancreatic Cancer

Concurrent chemoradiation using conventional fractionation (50.4–54 Gy in 1.8–2 Gy per fraction) in the definitive treatment of locally advanced unresectable PDAC remains controversial due to conflicting results from early randomized studies [7–9].

In the ECOG prospective trial, Loehrer et al. [9] randomized 74 patients with localized unresectable PDAC to two treatment arms: gemcitabine alone (1000 mg/m^2 weekly) or concurrent chemoradiation (50.4 Gy in 28 fractions + gemcitabine 600 mg/m^2 weekly) followed by gemcitabine (1000 mg/m^2 weekly), and demonstrated a survival benefit with the addition of concurrent chemoradiation compared to gemcitabine alone (11.1 vs. 9.2 months, P = 0.017), with acceptable toxicity.

However, the more recent LAP07 phase III randomized trial (n = 442) demonstrated that consolidative concurrent chemoradiation using conventional fractionation (54 Gy in 30 fractions + capecitabine 800 mg/m^2 bid on days of radiation) after induction gemcitabine ± erlotinib significantly decreased local progression (32% vs. 46%, P = 0.03) in patients with unresectable pancreatic cancer, but did not improve overall survival (15.2 vs. 16.5 months, P = 0.83) compared to systemic therapy in locally advanced PDAC patients; there was no increase in grade 3/4 toxicity, except for nausea [10]. A single institution retrospective study (n = 323) from the MD Anderson Cancer Center (MDACC) showed that induction chemotherapy followed by concurrent chemoradiation confers better overall survival and

progression-free survival vs. concurrent chemoradiation alone (8.5 vs. 4.2 months, $P < 0.001$ and 11.9 vs. 6.4 months, $P < 0.001$ respectively) in locally advanced/unresectable PDAC patients [11]. There was no significant difference in local and distant recurrence or toxicity between the two groups [11]. Induction chemotherapy consisted of gemcitabine/cisplatin or gemcitabine alone; 5-FU (300 mg/m^2/day continuous infusion), capecitabine (800–900 mg/m^2 bid on days of radiation) or gemcitabine (350–400 mg/m^2 weekly) was used concurrently with radiotherapy. With respect to radiotherapy, 85% of the patients received 30 Gy in 10 fractions, whereas 11% of the patients received the conventional fractionation of 50.4 Gy in 28 fractions using a four-field technique. The treatment volume included the primary tumor and regional lymph nodes in 69% of the patients and only the primary tumor in 31% of the patients [11]. It is interesting to note that the improvement in overall survival and progression-free survival was achieved with 30 Gy being used in most patients. As the authors suggested, induction chemotherapy likely selected for patients with more favorable tumor biology as they did not progress during induction chemotherapy and were therefore more likely to benefit from consolidative concurrent chemoradiation.

It should be emphasized that the above clinical studies used older chemotherapy regimens. As such, the results cannot be extrapolated to the modern day setting when FOLFIRINOX or gemcitabine/nab-paclitaxel is often given to patients with locally advanced PDAC first before concurrent chemoradiation or SBRT alone is considered for consolidation. Prospective randomized trials that incorporate these modern chemotherapy regimens should be pursued in order to determine the true benefit of definitive/consolidative concurrent chemoradiation or SBRT in locally advanced, non-metastatic PDAC.

It is important to note that conventional fractionation radiotherapy (50.4 Gy in 28 fractions) commonly used in the majority of modern chemoradiation trials only delivers a biologically effective dose (BED) (Box 81.3) of 59.47 Gy. Krishnan et al. [12] showed that following induction FOLFIRINOX (5-FU/irinotecan/oxaliplatin) or gemcitabine-based chemotherapy, the radiotherapy regimen (concurrent with gemcitabine or capecitabine) that delivered a BED of >70 Gy vs. ≤70 Gy significantly improved overall survival (17.8 vs. 15.0 months, $P = 0.03$) and locoregional recurrence free survival (10.2 vs. 6.2 months, $P = 0.05$) in patients with unresectable pancreatic cancer. The hypofractionation regimens used by the investigators for locally advanced/unresectable PDAC consisted of 63–70 Gy in 28 fractions if the tumor was ≤1 cm from luminal gastrointestinal (GI) structures, or 67.5 Gy in 15 fractions if the tumor was >1 cm from luminal GI structures, and incorporated a simultaneous integrated boost to deliver a BED of 77.2–97.9 Gy with intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) (Box 81.4) [12, 13]. To deliver these high BEDs, motion management and daily image guidance for radiotherapy delivery are critical. For instance, feedback guided inspiratory breath hold gating can be used during simulation and treatment for motion management, and CT-on-rail can be utilized for daily treatment verification to ensure that luminal GI tissues do not fall into the high dose regions and that the target is covered adequately as planned [13]. With more efficacious chemotherapy

such as FOLFIRINOX and gemcitabine/nab-paclitaxel treating microscopic disease, consolidative concurrent chemoradiation may be considered in locally advanced/unresectable PDAC patients who do not have distant metastasis following induction chemotherapy.

Box 81.3 Definition of *Biologically Effective Dose* (BED)
A measure that aims to indicate quantitatively the biological effect of any radiotherapy treatment, taking account of changes in dose-per-fraction or dose rate, total dose and overall time.

Box 81.4 Definition of Radiation Techniques and Modalities
- ***Intensity Modulated Radiotherapy (IMRT)***:
  A form of radiotherapy where the dose is modulated precisely using small beamlets to shape the radiation dose.
- ***Volumetric Modulated Arc Radiotherapy (VMAT)***:
  A form of radiotherapy where the dose is modulated precisely using small beamlets to shape the radiation dose while the treatment head machine is rotating resulting in faster delivery.
- ***Stereotactic body radiotherapy (SBRT)***:
  A form of radiotherapy in which a high dose per fraction is delivered ranging from 1 to 5 fractions for the overall treatment course with daily image guidance to ensure accurate delivery.
- ***MR-Linac***:

A linear accelerator device equipped with an MRI scanner that provides real time imaging while radiotherapy is being delivered.

Stereotactic body radiotherapy (SBRT) using a single-fraction regimen (25 Gy in 1 fraction) in early studies demonstrated excellent local control rates of 94–100% at 1 year in locally advanced PDAC, but high rates of GI toxicity were observed especially when gemcitabine was used before and after SBRT [14–18]. Subsequently, multi-fraction SBRT (33 Gy in 5 fractions or 24–36 Gy in 3 fractions) with or without gemcitabine was investigated and shown to provide excellent local control with acceptable toxicity in patients with locally advanced and locally recurrent PDAC [18–24]. As such, SBRT is included as a treatment option in the 2019 National Comprehensive Cancer Network guidelines for these PDAC patient populations. However, long-term survival benefit was not demonstrated with the multi-fraction SBRT regimen of 33 Gy in 5 fractions [20, 21], which delivers a BED of 54.78 Gy. It should be pointed out that while the prescription dose of most SBRT regimens is 30–45 Gy in 3–5 fractions, up to 30% of dose heterogeneity may be acceptable in the SBRT plans, resulting in a large percentage of the planning target volume

receiving a BED of 80–100 Gy [18]. As systemic therapy becomes more efficacious in controlling distant metastasis, it is conceivable that radiotherapy may play an increasingly important role in providing durable locoregional tumor control, which is achievable with radiation dose escalation and modern treatment techniques such as VMAT, SBRT, and MR-LINAC (Box 81.4). Importantly, apart from local control, SBRT has also been shown to reduce pancreatic pain significantly ($P < 0.001$) on the EORTC QLQ-PAN26 questionnaire at 4 months post treatment in patients with borderline resectable and locally advanced pancreatic cancer [18, 21]. Quality of life as determined by QLQ-C30 global QoL scores was reported to be stable from baseline to 4 months after SBRT [21].

The American Society for Radiation Oncology (ASTRO) published the 2019 clinical practice guidelines for radiation therapy in pancreatic cancer [25], which conditionally recommended a definitive treatment regimen consisting of systemic chemotherapy followed by concurrent chemoradiation using conventional fractionation or dose-escalated radiotherapy, or multifraction SBRT alone in patients with locally advanced disease not appropriate for downstaging to eventual surgery. With respect to dose fractionation, the 2019 ASTRO clinical practice guidelines [25] conditionally recommended 50.4–56 Gy in 1.75–2.2 Gy fractions for conventional fractionation and dose-escalation radiotherapy, and strongly recommended 33–40 Gy in 6.6–8 Gy fractions for SBRT. In terms of target volumes, the 2019 ASTRO clinical practice guidelines [25] conditionally recommended elective nodal coverage for concurrent chemoradiation using conventional fractionation radiotherapy, and strongly recommended including the gross tumor volume with a small margin in the treatment volume and not routinely treating elective lymph nodes for SBRT.

81.3 Palliative Radiotherapy for Symptom Management in Pancreatic Cancer

Before discussing radiotherapy, it is important to acknowledge the role of other specialties in providing palliation for patients with pancreatic cancer. Table 81.1 shows a summary of the involved medical specialties and the interventions they can provide, which will be addressed in other chapters of this book. In a

Table 81.1 Medical specialties and pertinent interventions for pancreatic cancer

Specialty	Intervention
Radiation oncology	– Radiation therapy for pain, bleeding or biliary obstruction
Medical oncology	– Chemotherapy
Hepato-pancreatico-biliary surgery	– Surgical bypass
Gastroenterology	– Biliary stent
Interventional radiology	– Percutaneous biliary drain – Celiac plexus neurolysis
Palliative care	– Pharmacotherapy for pain

population-based study by Tung et al. [26], it was noted that out of 2623 patients with unresectable pancreatic cancer, 61.8% of these patients reported a high Edmonton Symptom Assessment System (ESAS) pain score of 4 or more. Yet, Kulaylat et al. [27] showed that in 68,075 palliative patients, only 8% of patients received palliative radiotherapy, while 37% received chemotherapy.

The challenges of providing prospective empirical data regarding palliative endpoints include difficulty with recruiting patients into these studies and short endpoints due to the poor prognosis of this patient cohort [28]. Another challenge is measuring the end-point itself. Assessing overall survival in the palliative setting can be done, but is not the primary goal. Measuring symptom relief is often subjective and dependent on the patient, although there are standardized questionnaires that can be used such as EORTC QLQ-C30, EORTC QLQ-PAN26 and FACT-G [29, 30]. Another element to take into consideration is the heterogeneity of the radiation dose being delivered. The total dose of radiation is split into fractions. An abbreviated course of radiation therapy often, but not always, has a lower total dose than a protracted regimen.

A retrospective study conducted by Wolny-Rokicka et al. [31] evaluated palliative radiotherapy in 31 pancreatic cancer patients, measuring overall survival, toxicity, and pain relief. Pain relief was measured on a 0–3 WHO pain scale. Palliative radiotherapy was effective in 94% of patients at 4 weeks, resulting in either adequate pain control without pharmacotherapy or a reduction in the use of analgesics. All patients received upfront palliative chemotherapy prior to getting palliative radiation. There was significant heterogeneity in the radiotherapy regimens, with the shortest being 6 Gy in 1 fraction, and the longest being 30 Gy in 10 fractions. There was no statistical analysis conducted to derive any relationship between dose and pain relief. Overall survival at 1 year was 16%. Pain relief data was not captured at another interval, nor was there mention of the need for re-treatment.

Another study by Tian et al. [32] examined the use of SBRT in the palliation of pain and abdominal discomfort in 31 patients. The dose of radiation was 40–42 Gy in 7–8 fractions. The brief pain inventory was used to measure the pain response and EORTC QLQ-C30 for quality of life. Patients answered the questionnaires 1 week before radiotherapy, then at 1 month and 3 months after radiotherapy. Twenty-eight patients completed the questionnaires, with 57% of patients noting an improvement in abdominal pain at 1 month. In terms of quality of life, 42.8% of patients reported an improvement. Furthermore, Su et al. [33] retrospectively examined the use of SBRT in the palliation of abdominal pain in patients with locally advanced/unresectable and/or metastatic pancreatic cancer. Twenty-five patients were included, of whom 16 had metastatic disease and 9 had locally advanced/unresectable disease. The dose ranged from 30–48 Gy in 3–4 fractions. Eighty percent of patients achieved pain relief following 2 weeks after completion of radiotherapy. Wang et al. [34] assessed the use of IMRT in patients with locally advanced/unresectable and/or metastatic pancreatic cancer. The dose ranged from 26.8–54 Gy in 10–30 fractions ranging between 1.8–3 Gy per fraction. Sixty-three patients were included and 44 patients had relief from abdominal/back pain. Twelve of those patients had severe pain on the visual analogue scale.

Considering the cause of pain, a study by Hammer et al. [35] included 21 patients with celiac plexus neuropathy, 86% of whom had pancreatic head adenocarcinoma. Nineteen patients received an ablative dose of 25 Gy in 1 fraction and two received 9 Gy x 5 fractions to the celiac axis with a 1 cm planning tumor volume expansion. Median pain (on a 10-point scale) was 6/10 before treatment, decreased to 2.3/10 at 3 weeks and 1.8/10 at 6 weeks. Seventy-six percent of patients experienced some form of pain relief and 33% experienced complete amelioration of pain. The previous results were from a single institution study, an international phase II study is underway. The intervention is 25 Gy in 1 fraction and the primary outcome is pain response within 3 weeks following the intervention.

For pancreatic cancer patients who develop local recurrence/progression after a course of definitive radiotherapy, re-irradiation may be considered in those with a long disease recurrence/progression-free interval in the absence of distant metastasis.

The safety and efficacy data for re-irradiation is sparse, however, a retrospective study conducted by the MD ACC [36] evaluated 24 patients who were re-irradiated having had previous radiotherapy to their upper gastrointestinal malignancies. The primary outcome was development of adverse events; 11 of the 24 patients had pancreatic adenocarcinoma. The initial radiotherapy course ranged from 45–50.4 Gy. The re-irradiation dose comprised of 39 Gy in 26 fractions, with 2 fractions delivered daily separated by a 6 hours interval. Thirteen out of the 24 patients had acute side effects, the majority of which were mild and did not require supportive therapy. One patient had an upper GI bleed and there were no deaths that directly resulted from re-irradiation. Pain relief was not the primary outcome in this study, however, re-irradiation was generally well tolerated and may be a treatment option in appropriately selected patients. Patients should always be counselled on the potential of increased risk of acute and late toxicities associated with re-irradiation.

81.4 Obstructive Jaundice in Pancreatic Cancer

The mainstay treatment of obstructive jaundice in pancreatic cancer is a stenting procedure or surgical bypass [37, 38]. However, stents can be displaced by tumor growth, resulting in complications and/or failure of the stent.

A pilot study by Yang et al. [39] tested using Iodine 125 brachytherapy seed strands (Figs. 81.2 and 81.3 [40]) to palliate obstructive jaundice, via a trans-hepatic approach to stenting, with the strand inserted through the stent. Eighteen patients had the procedure done, with a mean dose of 167.2 Gy. The mean and median obstruction-free survival times were approximately 10 and 7 months, respectively. Only one patient suffered from stent obstruction at the 17 months mark most likely reflecting the poor overall survival of this disease entity. This pilot study demonstrated the safety of this modality, but further trials are warranted to compare this with standard therapies. There is a paucity of data regarding external beam radiation therapy and its use in relieving obstructive jaundice. This is most likely due to the fact that the effect of radiation is protracted; for immediate palliation, a mechanical solution is the first line of therapy [41].

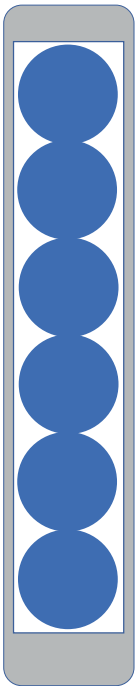

Fig. 81.2 Iodine 125 strand illustration. 4.5 mm × 0.8 mm capsule with 0.5 mm seeds

Fig. 81.3 Picture of the Iodine 125 seeds

81.5 Conclusion

Definitive radiotherapy can be utilized to provide local control in patients with locally advanced/ unresectable, non-metastatic pancreatic cancer and the role of radiotherapy in this patient cohort is evolving. Palliative radiotherapy can also be used to safely alleviate pain from pancreatic cancer. Multiple treatment regimens and radiotherapy techniques have proven effective and there is emerging data that

irradiating the celiac axis can be used to alleviate pancreatic neuropathy. Careful history taking, assessment of functional status, interdigitating radiation with systemic therapy, and multidisciplinary discussion all play a role in choosing the radiotherapy target and dose fractionation scheme to alleviate pain. Further studies are required to help elucidate which regimens should be offered as standard of care.

References

1. Wilkowski R, Wolf M, Heinemann V. Primary advanced unresectable pancreatic cancer. Recent Results Cancer Res. 2008;177:79–93.
2. Weledji EP, Enoworock G, Mokake M, Sinju M. How grim is pancreatic cancer? Oncol Rev. 2016;10:294.
3. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: techniques and results. Radiat Oncol. 2019;14:95.
4. Lutz S, et al. Palliative radiotherapy: when is it worth it and when is it not? Cancer J. 2010;16:473–82.
5. Habberstad R, et al. The Palliative Radiotherapy and Inflammation Study (PRAIS) – protocol for a longitudinal observational multicenter study on patients with cancer induced bone pain. BMC Palliat Care. 2018;17:110.
6. Glicksman RM, et al. Stereotactic ablative radiotherapy for the management of spinal metastases: a review. JAMA Oncol. 2020; https://doi.org/10.1001/jamaoncol.2019.5351.
7. Moertel CG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer. 1981;48:1705–10.
8. Chauffert B, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol. 2008;19:1592–9.
9. Loehrer PJ Sr, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 2011;29:4105–12.
10. Hammel P, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 Randomized Clinical Trial. JAMA. 2016;315:1844–53.
11. Krishnan S, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer. 2007;110:47–55.
12. Krishnan S, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. Int J Radiat Oncol Biol Phys. 2016;94:755–65.
13. Crane, C. H. Hypofractionated ablative radiotherapy for locally advanced pancreatic cancer. J Radiat Res57 Suppl 1, i53–i57 (2016).
14. Schellenberg D, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2008;72:678–86.
15. Chang DT, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer. 2009;115:665–72.

16. Schellenberg D, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011;81:181–8.
17. Trakul N, Koong AC, Chang DT. Stereotactic body radiotherapy in the treatment of pancreatic cancer. Semin Radiat Oncol. 2014;24:140–7.
18. Rosati LM, Kumar R, Herman JM. Integration of stereotactic body radiation therapy into the multidisciplinary management of pancreatic cancer. Semin Radiat Oncol. 2017;27:256–67.
19. Moningi S, et al. Stereotactic body radiation therapy for pancreatic cancer: single institutional experience. J Clin Oncol. 2014;32:328.
20. Pollom EL, et al. Outcomes and toxicity of SBRT for patients with unresectable pancreatic adenocarcinoma. J Clin Oncol. 2014;32:317.
21. Herman JM, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121:1128–37.
22. Mahadevan A, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys. 2011;81:e615–22.
23. Petrelli F, et al. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. Int J Radiat Oncol Biol Phys. 2017;97:313–22.
24. Moningi S, et al. The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience. Ann Surg Oncol. 2015;22:2352–8.
25. Palta M, et al. Radiation therapy for pancreatic cancer: executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol. 2019;9:322–32.
26. Tung S, et al. Population-based study of the prevalence and management of self-reported high pain scores in patients with non-resected pancreatic adenocarcinoma. Br J Surg. 2019;106:1666–75.
27. Kulaylat AS, Mirkin KA, Hollenbeak CS, Wong J. Utilization and trends in palliative therapy for stage IV pancreatic adenocarcinoma patients: a U.S. population-based study. J Gastrointest Oncol. 2017;8:710–20.
28. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. J Clin Oncol. 2014;32:2913–9.
29. Luckett T, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Ann Oncol. 2011;22:2179–90.
30. Fitzsimmons D, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100:918–26.
31. Wolny-Rokicka E, et al. Tolerance and efficacy of palliative radiotherapy for advanced pancreatic cancer: a retrospective analysis of single-institutional experiences. Mol Clin Oncol. 2016;4:1088–92.
32. Tian Q, Zhang F, Wang Y. Clinical assessment of palliative radiotherapy for pancreatic cancer. Cancer Radiother. 2018;22:778–83.
33. Su T-S, et al. Stereotactic body radiotherapy using CyberKnife for locally advanced unresectable and metastatic pancreatic cancer. World J Gastroenterol. 2015;21:8156–62.
34. Wang Z, et al. Intensity modulated radiotherapy for locally advanced and metastatic pancreatic cancer: a mono-institutional retrospective analysis. Radiat Oncol. 2015;10:14.
35. Hammer L, et al. Celiac plexus radiosurgery, a new modality for cancer pain management – final results of a phase II clinical trial. Int J Radiat Oncol Biol Phys. 2018;102:S38.
36. Hunt A, et al. Hyperfractionated abdominal reirradiation for gastrointestinal malignancies. Radiat Oncol. 2018;13:143.

37. Tsuyuguchi T, et al. Stenting and interventional radiology for obstructive jaundice in patients with unresectable biliary tract carcinomas. J Hepatobiliary Pancreat Surg. 2008;15:69–73.
38. Gouma DJ, Busch ORC, Van Gulik TM. Pancreatic carcinoma: palliative surgical and endoscopic treatment. HPB. 2006;8:369–76.
39. Yang M, et al. A pilot study of intraluminal brachytherapy using 125I seed strand for locally advanced pancreatic ductal adenocarcinoma with obstructive jaundice. Brachytherapy. 2016;15:859–64.
40. LDR Iodine-125 seeds for prostate & brain – Oncology Systems Limited. *Oncology Systems Limited*. https://osl.uk.com/radiotherapy/treatment-delivery/hdr-iodine-125-seeds-for-prostate-brain/.
41. Park S, et al. Radiotherapy prolongs biliary metal stent patency in malignant pancreatobiliary obstructions. Gut Liver. 2013;7:480–5.

Chapter 82
Role of Ablation Technologies in Locally Advanced Pancreatic Cancer

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Take Home Messages

- Ablation technologies have emerged as a therapeutic option for locally advanced pancreatic cancer with tumours not suitable for surgery after systemic treatment.
- Several ablation strategies are available and are generally divided into thermal and non-thermal approaches.
- Post-procedure complications are common and can be serious and even life-threatening. Ablation procedures are best performed only at high-volume centres of pancreatic surgery.
- Current research shows encouraging results; however, randomized control trials and sufficiently powered multicentre studies are required to confirm their efficacy.

Pearls and Pitfalls

- Ablation technologies may represent a valid therapeutic option for the vast majority of patients with locally advanced pancreatic cancer who will not receive surgical exploration.
- Ablation is performed using different types of energy delivered through single or multiple probes and some in a minimally invasive fashion.

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- Radiofrequency ablation (RFA) and Irreversible Electroporation (IRE) are the two most adopted ablation techniques.
- Well-selected patients with locally advanced pancreatic cancer may benefit from ablation technologies, at the price of reasonable rates of morbidity (25–30%) and mortality (about 2%).

Future Perspectives
- Further effort should be made to investigate predictive factors associated with the local response after ablation.
- Role of novel technologies, including electrochemical therapy and laser, needs further investigation.
- Studies into patient selection for optimal treatment response is warranted.

82.1 Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide, with a 5-year survival rate of approximately 5–8% [1]. Surgery remains the only potentially curative treatment option; however, only 20% of patients are candidates for radical surgical resection at the time of diagnosis. Locally advanced pancreatic cancer (LAPC) is one of the most diagnosed stages, comprising 30–40% of cases [2] (stage III of the eighth American Joint Committee on Cancer Classification [3]).

The best therapeutic approach for the treatment of LAPC is systemic therapy. FOLFIRINOX, a combination chemotherapy comprising fluorouracil, leucovorin, irinotecan, and oxaliplatin, or gemcitabine and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) are favoured to increase the rates of conversion to surgery and overall survival (OS) [4, 5]. According to the National Comprehensive Cancer Network (NCCN) guidelines, radiotherapy may be considered and can sterilise vessel margins to improve R0 resection, or as second-line therapy for patients with local progression but without distant metastasis [6].

Unfortunately, only a small percentage of patients achieve downstaging and become suitable candidates for surgery after therapy. The literature reports of heterogeneous proportions, with the majority within 10–35% [7–9]. In our recent observational study, the resection rate of LAPC patients was only 9%, with a resection/exploration rate of 48% [10]. This finding is not surprising when one considers the natural history of LAPC. In most cases, the disease has progressed to metastasis at the time of restaging after chemotherapy or remained stable or downsized, maintaining local involvement of vascular structures. In this scenario, there is a lower chance of R0 resection and may come with the cost of increased surgical risks. A meta-analysis performed in the pre-FOLFIRINOX era showed an increased risk of perioperative mortality and no 1- and 3-year survival benefit for patients with arterial resection, which was also confirmed when compared to patients undergoing venous resection [11]. In high-volume centres, consistent rates of postoperative morbidity and

mortality have been recently reported; however, not all studies demonstrated encouraging rates of margin-free surgery [12, 13]. In addition, the prescribed neoadjuvant chemotherapy is not tolerated and completed by all patients, mainly because of toxicity [9, 14, 15], thus impeding any attempt of tumour downsizing or downstaging.

Altogether, ablation technologies have emerged as an interesting therapeutic option for LAPC in patients unsuitable for surgical resection after systemic treatment.

82.2 Rationale for the Use of Ablation Technologies

Local ablation techniques have been introduced as a weapon for the treatment of LAPC that is not amenable to surgical resection, primarily because of their potential role in inducing citoreduction [16], maintaining local disease control, and potentially stimulating an immune response against the tumour [17–20]. They have also been demonstrated to play an important role in palliative care to reduce cancer pain [21]. A further and yet unexplored interesting field of application of ablation strategies is the potential for their application in patients that are not suitable for surgery or multidrug chemotherapy regimens because of comorbidities.

82.3 General Features of Local Ablative Therapies and Indications for Treatment

According to the type of energy used and the effects on tissues, ablation strategies can be classified as thermal and non-thermal. This chapter presents the most frequently adopted ablative techniques for which robust data is present, comprising radiofrequency ablation (RFA), high-intensity focus ultrasound (HIFU), and irreversible electroporation (IRE). Novel ablative techniques currently being investigated are also presented. Table 82.1 presents a summary of the main features of the different ablation strategies. Radiotherapy is not included, as it does not represent an appropriate ablative technique.

For the majority of techniques, the approach adopted (laparotomic, laparoscopic, percutaneous, or endoscopic) is at the discretion of the user (surgeon, interventional radiologist, or gastroenterologist), and should be selected based on the training and expertise of the professional, as well as on facilities available. Indeed, post-procedure complications are common and can be comparatively serious to those occurring after pancreatic surgery [22]. Therefore, only high-volume centres should adopt these techniques.

Anatomically, the location of the pancreas, which is surrounded by vital structures or precious organs, discourages per sé any oncological intervention or procedure. In LAPC, this is somewhat heightened by tumour infiltration of these structures, which partially prevents complete treatment from avoiding collateral damage.

Table 82.1 Summary of the main features of the various ablative techniques

Ablative technique	Type of energy	Damage induced	Approach	Contraindications
RFA	High-frequency alternating current	Coagulative necrosis, tissue coagulation, and protein denaturation	Laparotomy, laparoscopy, endoscopy, percutaneous	Involvement of duodenum or major vessels, metallic stents
IRE	Local electric fields	Apoptosis, irreversible permeabilisation of cell membranes	Laparotomy, percutaneous	Arrhythmias, pacemaker/implantable cardioverter defibrillator, potentially metallic stents
HIFU	Ultrasound energy	High-temperature damage	Extracorporeal	
ECT	Local electric fields	Permeabilization of cellular membrane to drug	Laparotomy, percutaneous	Arrhythmias, pacemaker/implantable cardioverter defibrillator, epilepsy
Laser	Laser energy	Necrosis	Laparotomy, endoscopy	

RFA radiofrequency ablation, *IRE* irreversible electroporation, *HIFU* high-intensity focused ultrasound, *ECT* electrochemotherapy

82.4 Radiofrequency Ablation (RFA)

RFA is a thermal technique based on high-frequency alternating currents conducted by needle electrodes inserted in the core of the tumour, producing necrosis through tissue coagulation and protein denaturation. Temperatures can reach up to 105 °C with the procedure ranging from 5–15 min [23, 24]. To reduce the risk of damage to the surrounding structures, a safety distance of 10–15 mm from the duodenum and the mesentericoportal axis is required [25]. The procedure can be performed via a laparotomic, laparoscopic, percutaneous, and endoscopic approach [26]. A mass-forming pancreatic cancer represents the best LAPC to treat with RFA, potentially using a minimally invasive approach. A percutaneous approach is preferred if the tumour is located in the tail of the pancreas, whereas endoscopic ablation is generally performed for pancreatic head cancer [16, 27]. These approaches minimise the stress associated with laparotomy.

Through ultrasound monitoring, a real-time evaluation can be performed, as gas bubbles can be detected during ablation (Fig. 82.1a). Furthermore, ultrasound enables the detection of damage within the tumor and, if required, ablation can be repeated by reinserting the needle in another part of the lesion. For unplanned procedures, the simplicity of the technique allows its adoption as a *salvage procedure* in cases that are not radically resectable intraoperatively [28].

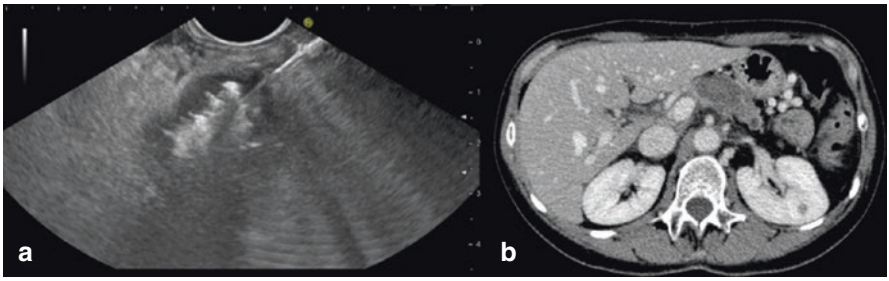

Fig. 82.1 (**a**) Gas bubbles formation during an endoscopic ablation of LAPC within the center of the tumor. (Courtesy of Dr. Stefano Francesco Crinò, MD.) (**b**) One-month triple-phase contrast-enhanced CT-scan showing post-ablation necrotic area. (Courtesy of Prof. Mirko D'Onofrio)

82.4.1 Oncological Outcomes

Due to the lack of large multicentre studies and randomised controlled trials, oncological results reported so far are debatable. A recent review reported an OS ranging between 19 and 25.6 months [22]. These promising results are from studies with well-selected patient cohorts, and the selection bias may represent a major factor influencing the results.

82.4.2 Post-Procedure Course

Major complications after RFA are possible and mainly related to the thermal energy employed during the procedure. These include pancreatic fistula, acute pancreatitis, portal vein thrombosis, duodenal and biliary thermal injury, gastric ulcer or fistula, and post-operative haemorrhage [22]. Technical tricks may help in reducing the incidence of post-procedure complications, such as duodenal cooling, safe ablation margins, and the selection of cases; however, the outcomes cannot exclude the users' experience. In a recent series performed in our institute on percutaneous RFA for LAPC, no complications were reported in the 23 patients examined [16].

82.5 Irreversible Electroporation (IRE)

IRE emerged as the counterbalance of RFA, as it is more likely applied to LAPC than RFA due to its non-thermal mechanism of action. Consequently, numerous studies have been performed over recent years [29]. IRE induces cell death *via* apoptosis through the application of local electric fields that irreversibly

permeabilise cell membranes. It is a multiprobe technique requiring several needle electrodes [30]. The most widely adopted approach is the laparotomy; however, the percutaneous approach is gaining interest [30]. Tumours should have a maximum diameter of 4 cm, an optimal probe exposure of 1.5 cm, and a distance of 1–2 cm (minimum to maximum) between the probes [31].

For its physical basis, the IRE has several advantages compared to RFA. Changes in the transmembrane potential leading to lipid bilayer disruption appear to occur almost exclusively in tumour cells, preserving surrounding vital structures such as blood vessels [32]. While the ideal tumour to treat with RFA is the mass-forming type, tumours running as a *cast* along the major peripancreatic vessels may also be treated using IRE [33], with a potential two to three pullbacks of the needle electrodes and multiple IRE sessions. Other advantages include lack of the *heat sink effect*, which may affect the efficacy of the thermal ablation procedure, and the sparing of tissue architecture [32].

For the above-mentioned features, IRE has been adopted with a double aim: as an *in situ* treatment offering local control of the disease in LAPC patients not considered to be suitable for radical surgery, and in conjunction with surgical resection (IRE with *margin accentuation*). The first aim has been mainly explored, demonstrating that IRE may offer consolidative disease control with symptom relief and pain control [34].

IRE is more difficult to apply than RFA. The procedure requires in-depth skills of interventional radiology and precise preoperative planning, preventing it from being considered as a *salvage procedure* in scenarios of intraoperative unresectability [28].

Because of the use of electric fields, arrhythmias and pacemaker/implantable cardioverter defibrillators are absolute contraindications. Less severe cardiac comorbidities represent potential relative contraindications, while the presence of a metallic stent should not be considered a contraindication by default. However, if the ablation zone does not include the stent, IRE can be performed safely.

82.5.1 Oncological Outcomes

A recent prospective, multi-institutional study from the AHPBA Pancreatic Registry evaluated 152 patients who underwent open IRE. The median OS from diagnosis was 30.7 months, and the median progression-free survival (PFS) time was 22 months [35]. In a recent review analysing 43 studies comprising a total of 498 patients undergoing open, percutaneous, or laparoscopic IRE, the median OS after IRE varied from 7 to 27 months, whereas the median PFS ranged from 5 to 15 months [29, 36]. When compared with patients that underwent chemotherapy and/or radiation therapy only, patients that underwent IRE showed an improved OS from 11 to 20.2 months, improved PFS, and distant PFS [37]. Interestingly, cases of post-IRE downstaging to resection were reported [38–40]. Notably, IRE does not appear to provide any survival benefit when applied upfront [41].

82.5.2 Post-Procedural Course

The AHPBA Pancreatic Registry reported morbidity and mortality rates of approximately 27% and 2%, respectively [35]. Interestingly, the systematic review of Moris et al. reports cumulative overall morbidity and mortality rates of 30% and 2.2%, respectively [29]. In a systematic review, pooled prevalence rates of pancreatic fistula, pancreatitis, and post-IRE haemorrhage were reported to be 10.6%, 7.2%, and 4.2%, respectively [42]. These numbers highlight potential serious post-IRE complications and indirectly mark the importance of user expertise and the facilities of the adopting centre.

82.6 High-Intensity Focus Ultrasound (HIFU)

HIFU destroys tumour cells by increasing local tissue temperatures to up to 65 °C using focused ultrasound energy from an extracorporeal source [43]. It can be performed in two different patterns according to the ultrasound type selected. Continuous HIFU induces coagulative necrosis of targeted tissues, using high-intensity ultrasound in a single session. However, because of the pain and the discomfort associated with this approach, patients require sedation or general anaesthesia, and need to be hospitalised for several days. In contrast, pulsed HIFU uses low-intensity ultrasound and requires several sessions, with patients not requiring sedation or hospitalization [44]. HIFU therapy has several advantages over other ablation techniques. It does not require incisions or percutaneous needle electrode placement. Furthermore, recovery times are short. In addition, a reduction in mortality, morbidity, and hospital stays, as well as an improvement in quality of life have been demonstrated [45].

Acceptable rates of post-HIFU morbidity (0–23%) were reported recently. The most common and relevant complications were skin burns, subcutaneous fat sclerosis, gastrointestinal ulcer or bleeding, abdominal pain, and pancreatic fistula or pseudocyst [22]. The OS ranged from 6 to 14 months. Major benefits have been reported when combining HIFU and chemotherapy compared to HIFU alone [46].

82.7 Novel Ablative Therapies

A number of novel ablative therapies are currently under investigation. These strategies have either unique peculiarities, such as laser ablation, or share a feature with more commonly adopted techniques, such as electrochemotherapy. These strategies are presented briefly, as only very few reports are available.

82.7.1 Electrochemotherapy (ECT)

ECT shares identical physical principles with IRE. Through the application of local electric fields using needle electrodes and a generator, cell membrane permeabilization is induced. In contrast to IRE, this phenomenon is reversible in electrochemotherapy. The pores produced facilitate intracellular entry of intravenously administered drugs administered almost concomitantly, e.g., bleomycin for pancreatic cancer. Consequently, pore closure ensures local concentration-dependent cytotoxic effects of the drug [47]. ECT is a multiprobe technique and requires in-depth preoperative planning to create optimal geometric configuration of the needle electrodes. There are only few clinical studies on LAPC; however, preliminary results demonstrate the safety and feasibility of the procedure [48], which deserves further investigation.

82.7.2 Laser Treatment

This new technique has a few clinical applications in LAPC [49, 50]. Currently, there is an ongoing phase I study at our institute (NCT02702986) using the immunostimulating interstitial laser thermotherapy (imILT®) and another one is running in Marseille, France (#NCT02973217). Several preclinical models demonstrated that the low temperature and power laser could elicit a systemic antitumor immune response [51]. The technique can be classified as a thermal technique. Briefly, the system comprises a laser generator that is connected to an optical fibre, which is introduced into the tumour using a needle guide, and at least one temperature feedback probe. This system generates heat by the absorption of light in the tissue, producing an ovoid-shaped ablation [28]. The laser technique is relatively easy to use; therefore, RFA can be considered a salvage procedure if unresectability is confirmed intraoperatively.

82.8 Complications of Ablation of LAPC

All techniques may cause collateral damage. This concept becomes essentially "normal" when considering that, by definition, LAPC involves vital structures. Therefore, any attempt of tumour ablation may expose patients to a higher risk of unintentional injuries.

Complications may be severe and life-threatening [22], as any visceral or vascular injury is the result of thermal damage to the tissue, which has an unpredictable fate in terms of scar evolution. The mortality rate can reach up to 5% [52, 53].

In addition, the pancreatic parenchyma is particularly sensitive to thermal injury and may respond with an inflammation response that could lead to severe

pancreatitis and damage to surrounding structures. Of note, heat may activate the endothelium contributing to procoagulative effects, leading to primarily venous but also arterial thrombosis [54]. This phenomenon has been reported for thermal techniques such as RFA and IRE with unclear pathophysiology.

The management of post-procedure complications may be quite complex and involve interventional radiologists, gastroenterologists, experienced pancreatic surgeons, and intensivists. This highlights the importance of high quality and well-coordinated facilities.

An overview of the major complications of the main techniques discussed in this chapter is shown in Table 82.2. Reports are from recently performed studies.

82.9 Post-Procedure Follow-Up

The correct interpretation of radiologic examinations is fundamental for assessing a positive response to treatment and detecting disease recurrence. The vast majority of data available stems from experience with RFA and IRE.

To evaluate the resulting ablated area in RFA, dynamic examination after contrast agent injection is usually performed 1 month after the procedure, as it is possible to detect the effects of thermally-induced necrosis [24]. Early examination

Table 82.2 Major complications after RFA, IRE, and HIFU

Complications	RFA		IRE		HIFU	
	Y/N	%	Y/N	%	Y/N	%
Pancreatitis	Yes	0–3.3 [16, 55–57]	Yes	4–14 [58–60]	Yes	2–15 [61–63]
Pancreatic fistula	Yes	0–3 [16, 55–57]	Yes	2.4–12 [60, 64]	Yes	4 [63]
Pseudocyst	No		No		Yes	6 [62]
Duodenal ulcer/ perforation	Yes	0–4.4 [16, 55–57]	Yes	4 [58]	No	
Gastric ulcer/perforation	No		Yes	2 [40]	Yes	2–12.5 [63, 65]
Portomesenteric thrombosis	Yes	0–4 [16, 55–57]	Yes	4–10 [58–60, 66]	No	
Arterial thrombosis	No		Yes	2 [67]	No	
Abdominal abscess	Yes	0–5 [16, 55]	Yes	1.9–9.5 [64, 68]	No	
Pseudoaneurysm	No		Yes		No	
Biliary obstruction	No		Yes	5.3–6% [53, 69]	No	
Arterio-enteric fistula	No		Yes [70]		No	

RFA radiofrequency ablation, *IRE* irreversible electroporation, *HIFU* high-intensity focus ultrasound

using a contrast-enhanced CT scan is performed 1 day after the procedure, primarily to rule out potential complications rather than to evaluate the ablation effect. Arterial and venous phases play an important role in detecting vascular complications such as pseudoaneurysms and venous thrombosis, with the late phase the best for measuring the ablated area [24] (Fig. 82.1b). Vessel thrombosis, occlusion, or distortion have been reported in post-RFA CT scans; however, no clinical sequelae have been associated with these events [71].

Post-IRE imaging usually demonstrates an area larger than the ablated tumour as a result of acute procedural-related inflammation. However, the ablated area could be rather difficult to measure because of the consistency of the surrounding tissue [72]. In the months following IRE, the ablated area generally decreases, with the consolidation of the inflammatory processes until a stable size is achieved [72].

For both techniques, an increase in the tumour size or the ablation area after a period of stability, in conjunction with increased carbohydrate antigen 19.9 (CA 19.9) with or without clinical progression, must be suspected in disease progression. Of note, increased CA 19.9 levels may be observed in the postoperative period [16], without early disease progression. Therefore, variations of CA 19.9 levels should be interpreted cautiously and integrated with other instrumental or clinical elements.

82.10 Future Considerations

Despite progress in medical and surgical oncology, pancreatic cancer remains a tumour with a dismal prognosis, and surgery followed by adjuvant chemotherapy is the only curative strategy. However, due to late diagnosis, only a small number of patients can receive radical surgery at the time of diagnosis. For these patients, the only valid therapeutic path is chemotherapy with or without radiotherapy, potentially followed by surgery. However, the conversion rate in surgery remains low. In this scenario, local ablation strategies offer patients an alternative therapy that may help in inducing cytoreduction and in obtaining local control of the disease. These strategies should be considered as an adjunctive weapon for LAPC treatment within multimodal therapeutic management.

The oncological outcomes reported so far are heterogeneous and not entirely encouraging, which comes as no surprise, as such outcomes are also observed for surgery or conventional and consolidated chemotherapy. This is associated with the biology of pancreatic cancer that may tend towards early systemic diffusion or indolent local growth. In this regard, analysing the growth pattern of a LAPC with a tendency to a local growth than a systemic spread, potentially in association with biological tools such as *SMAD4* gene status assessment [73], may help to identify tumours that may benefit from local ablation. Unquestionably, these approaches should not be applied upfront but in properly designed trials.

82.11 Conclusions

Further effort should be made to investigate predictive factors associated with the local response after ablation. Patients with LAPC patients that are not reconsidered for surgical resection require feedback, and ablative cytoreduction is often the only means of obtaining local control of the disease as well as potentially ameliorating the patients' quality of life.

Ablation strategies should no longer be considered as *the last resort* for LAPC patients, rather a dedicated therapy for selected ones. The urge for thoroughly investigating the presumable immunostimulating effect that can be obtained using ablative techniques arises [19], as it potentially represents the keystone treatment for such patients. Proper clinical trials are required in this particular setting.

The still dismal prognosis of LAPC imposes further research on ablation techniques. Until the availability of randomized controlled trials, ablative technologies will continue to be adopted in selected cohorts of patients with LAPC.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018: cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. van Veldhuisen E, et al. Locally advanced pancreatic cancer: work-up, staging, and local intervention strategies. Cancers. 2019;11:976.
3. Chun YS, Pawlik TM, Vauthey J-N. Eighth edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. Ann Surg Oncol. 2018;25:845–7.
4. Suker M, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17:801–10.
5. Hammel P, et al. Phase II LAPACT trial of *nab*-paclitaxel (*nab*-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC). J Clin Oncol. 2018;36:204.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Pancreatic adenocarcinoma. NCCN Guidelines version 3.2017.
7. Reni M, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol. 2017;28:2786–92.
8. Gemenetzis G, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg. 2019;270:340–7.
9. Marthey L, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015;22:295–301.
10. Maggino L, et al. Outcomes of primary chemotherapy for borderline resectable and locally advanced pancreatic ductal adenocarcinoma. JAMA Surg. 2019;154(10):932–42. https://doi.org/10.1001/jamasurg.2019.2277.
11. Mollberg N, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. Ann Surg. 2011;254:882–93.
12. Bachellier P, Addeo P, Faitot F, Nappo G, Dufour P. Pancreatectomy with arterial resection for pancreatic adenocarcinoma: how can it be done safely and with which outcomes? Ann Surg. 2020;271(5):932–40. https://doi.org/10.1097/SLA.0000000000003010.
13. Cannella R, Borhani AA, Zureikat AH, Tublin ME. Appleby procedure (distal pancreatectomy with celiac artery resection) for locally advanced pancreatic carcinoma: indications, outcomes, and imaging. AJR Am J Roentgenol. 2019:1–10. https://doi.org/10.2214/AJR.18.20887.

14. Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. Sci Rep. 2018;8:8666.
15. Baldini C, et al. Safety and efficacy of FOLFIRINOX in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma: a retrospective analysis. Pancreatology. 2017;17:146–9.
16. D'Onofrio M, et al. Percutaneous radiofrequency ablation of unresectable locally advanced pancreatic cancer: preliminary results. Technol Cancer Res Treat. 2017;16:285–94.
17. Giardino A, et al. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. Pancreatology. 2017;17:962–6.
18. He C, Wang J, Sun S, Zhang Y, Li S. Immunomodulatory effect after irreversible electroporation in patients with locally advanced pancreatic cancer. J Oncol. 2019;2019:1–13.
19. Zhao J, et al. Irreversible electroporation reverses resistance to immune checkpoint blockade in pancreatic cancer. Nat Commun. 2019;10:899.
20. Scheffer HJ, et al. Irreversible electroporation of locally advanced pancreatic cancer transiently alleviates immune suppression and creates a window for antitumor T cell activation. Oncoimmunology. 2019;8:1652532.
21. Carrafiello G, et al. Microwave ablation of pancreatic head cancer: safety and efficacy. J Vasc Interv Radiol. 2013;24:1513–20.
22. Ruarus A, Vroomen L, Puijk R, Scheffer H, Meijerink M. Locally advanced pancreatic cancer: a review of local ablative therapies. Cancers. 2018;10:16.
23. Fegrachi S, et al. Safety of radiofrequency ablation in patients with locally advanced, unresectable pancreatic cancer: a phase II study. Eur J Surg Oncol. 2019;45:2166–72.
24. D'Onofrio M, et al. Percutaneous ablation of pancreatic cancer. World J Gastroenterol. 2016;22:9661.
25. Fegrachi S, et al. Radiofrequency ablation of the pancreas with and without intraluminal duodenal cooling in a porcine model. J Surg Res. 2013;184:867–72.
26. Crinò SF, et al. EUS-guided radiofrequency ablation (EUS-RFA) of solid pancreatic neoplasm using an 18-gauge needle electrode: feasibility, safety, and technical success. J Gastrointestin Liver Dis. 2018;27:67–72.
27. Paiella S, et al. Palliative therapy in pancreatic cancer—interventional treatment with radiofrequency ablation/irreversible electroporation. Transl Gastroenterol Hepatol. 2018;3:80.
28. Paiella S, et al. Ablation treatments in unresectable pancreatic cancer. Minerva Chir. 2019;74:263–9.
29. Moris D, et al. Systematic review of surgical and percutaneous irreversible electroporation in the treatment of locally advanced pancreatic cancer. Ann Surg Oncol. 2019;26:1657–68.
30. Martin RCG. Use of irreversible electroporation in unresectable pancreatic cancer. Hepatobiliary Surg Nutr. 2015;4:211–5.
31. Martin RC, Irreversible G. Electroporation of locally advanced pancreatic head adenocarcinoma. J Gastrointest Surg. 2013;17:1850–6.
32. Young SJ. Irreversible electroporation and the pancreas: what we know and where we are going? World J Gastrointest Surg. 2015;7:138.
33. Paiella S, et al. Local ablative strategies for ductal pancreatic cancer (radiofrequency ablation, irreversible electroporation): a review. Gastroenterol Res Pract. 2016;2016:1–10.
34. Field W, Rostas JW, Martin RCG. Quality of life assessment for patients undergoing irreversible electroporation (IRE) for treatment of locally advanced pancreatic cancer (LAPC). Am J Surg. 2019;218:571–8.
35. Holland MM, et al. A prospective, multi-institution assessment of irreversible electroporation for treatment of locally advanced pancreatic adenocarcinoma: initial outcomes from the AHPBA pancreatic registry. HPB. 2019;21:1024–31.
36. He C, et al. Irreversible electroporation versus radiotherapy after induction chemotherapy on survival in patients with locally advanced pancreatic cancer: a propensity score analysis. BMC Cancer. 2019;19:394.

37. Martin RCG, McFarland K, Ellis S, Velanovich V. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. Ann Surg Oncol. 2013;20:443–9.
38. Leen E, et al. Percutaneous irreversible electroporation with systemic treatment for locally advanced pancreatic adenocarcinoma. J Gastrointest Oncol. 2018;9:275–81.
39. Belfiore MP, et al. Percutaneous CT-guided irreversible electroporation followed by chemotherapy as a novel neoadjuvant protocol in locally advanced pancreatic cancer: our preliminary experience. Int J Surg. 2015;21:S34–9.
40. Kluger MD, et al. Single-institution experience with irreversible electroporation for T4 pancreatic cancer: first 50 patients. Ann Surg Oncol. 2016;23:1736–43.
41. MåNsson C, et al. Percutaneous irreversible electroporation as first-line treatment of locally advanced pancreatic cancer. Anticancer Res. 2019;39:2509–12.
42. Tian G, Liu X, Zhao Q, Xu D, Jiang T. Irreversible electroporation in patients with pancreatic cancer: how important is the new weapon? Biomed Res Int. 2018;2018:1–12.
43. Chauffert B, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study. Ann Oncol. 2008;19:1592–9.
44. Dromi S, et al. Pulsed-high intensity focused ultrasound and low temperature sensitive liposomes for enhanced targeted drug delivery and antitumor effect. Clin Cancer Res. 2007;13:2722–7.
45. Ierardi AM, et al. Percutaneous ablation therapies of inoperable pancreatic cancer: a systematic review. Ann Gastroenterol. 2015;28:431–9.
46. Gao H-F, et al. High intensity focused ultrasound treatment for patients with local advanced pancreatic cancer. Hepatogastroenterology. 2013;60:1906–10.
47. Mir LM, et al. Standard operating procedures of the electrochemotherapy: instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator™ by means of invasive or non-invasive electrodes. Eur J Cancer Suppl. 2006;4:14–25.
48. Granata V, et al. Electrochemotherapy in locally advanced pancreatic cancer: preliminary results. Int J Surg. 2015;18:230–6.
49. Di Matteo FM, et al. Feasibility of EUS-guided Nd:YAG laser ablation of unresectable pancreatic adenocarcinoma. Gastrointest Endosc. 2018;88:168–174.e1.
50. Jiang T, Deng Z, Li J, Tian G. Pancreatic cancer: does it work if EUS and laser ablation get married? Endosc Ultrasound. 2018;7:207.
51. Axelsson J, et al. Initial findings of immunostimulating interstitial laser thermotherapy of solid tumours. J Clin Stud. 2017;9:28–31.
52. Flak RV, et al. Treatment of locally advanced pancreatic cancer with irreversible electroporation – a Danish single center study of safety and feasibility. Scand J Gastroenterol. 2019;54:252–8.
53. Scheffer HJ, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014;25:997–1011.
54. Ekici Y, Tezcaner T, Aydın HO, Boyvat F, Moray G. Arterial complication of irreversible electroporation procedure for locally advanced pancreatic cancer. World J Gastrointest Oncol. 2016;8:751.
55. Frigerio I, Giardino A, Grielli R, Regi P, Scopelliti F. RFA and pancreatic cancer: 5 years experience from a single center. Eur J Surg Oncol EJSO. 2013;39:S46.
56. Girelli R, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbecks Arch Surg. 2013;398:63–9.
57. Paiella S, et al. Role of local ablative techniques (radiofrequency ablation and Irreversible electroporation) in the treatment of pancreatic cancer. Updat Surg. 2016;68:307–11.
58. Månsson C, Brahmstaedt R, Nilsson A, Nygren P, Karlson B-M. Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. Eur J Surg Oncol EJSO. 2016;42:1401–6.

59. Narayanan G, et al. Percutaneous image-guided irreversible electroporation for the treatment of unresectable, locally advanced pancreatic adenocarcinoma. J Vasc Interv Radiol. 2017;28:342–8.
60. Zhang Y, et al. Percutaneous irreversible electroporation for ablation of locally advanced pancreatic cancer: experience from a Chinese institution. Pancreas. 2017;46:e12–4.
61. Ning Z, et al. HIFU is safe, effective, and feasible in pancreatic cancer patients: a monocentric retrospective study among 523 patients. Onco Targets Ther. 2019;12:1021–9.
62. Sofuni A, et al. Safety trial of high-intensity focused ultrasound therapy for pancreatic cancer. World J Gastroenterol. 2014;20:9570–7.
63. Sung HY, et al. Long-term outcome of high-intensity focused ultrasound in advanced pancreatic cancer. Pancreas. 2011;40:1080–6.
64. Martin RC, Philips P, Ellis S, Hayes D, Bagla S. Irreversible electroporation of unresectable soft tissue tumors with vascular invasion: effective palliation. BMC Cancer. 2014;14:540.
65. Li Y-J, Huang G-L, Sun X-L, Zhao X-C, Li Z-G. The combination therapy of high-intensity focused ultrasound with radiotherapy in locally advanced pancreatic carcinoma. World J Surg Oncol. 2016;14:60.
66. Paiella S, et al. Safety and feasibility of irreversible electroporation (IRE) in patients with locally advanced pancreatic cancer: results of a prospective study. Dig Surg. 2015;32:90–7.
67. Martin RCG, et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg. 2015;262:486–94.
68. Lambert L, et al. Treatment of locally advanced pancreatic cancer by percutaneous and intraoperative irreversible electroporation: general hospital cancer center experience. Neoplasma. 2016;63:269–73. https://doi.org/10.4149/213_150611N326.
69. Bhutiani N, et al. Safety, efficacy, and technical details of endoscopic retrograde cholangiopancreatography after irreversible electroporation for locally advanced pancreatic cancer. J Gastrointest Surg. 2020;24(5):1077–108. https://doi.org/10.1007/s11605-019-04223-y.
70. Lundy M, Garland-Kledzik M, Shen P. Arterio-enteric fistula after irreversible electroporation. Am Surg. 2019;85:e55–7.
71. Rombouts SJE, et al. Computed tomography findings after radiofrequency ablation in locally advanced pancreatic cancer. Abdom Radiol. 2018;43:2702–11.
72. Akinwande O, Ahmad SS, Van Meter T, Schulz B, Martin RCG. CT findings of patients treated with irreversible electroporation for locally advanced pancreatic cancer. J Oncol. 2015;2015:1–8.
73. Paiella S, et al. Radiofrequency ablation for locally advanced pancreatic cancer: SMAD4 analysis segregates a responsive subgroup of patients. Langenbecks Arch Surg. 2018;403(2):213–20. https://doi.org/10.1007/s00423-017-1627-0.

Chapter 83
Sonoporation to Enhance Drug Delivery in Metastatic Pancreatic Cancer

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Take Home Messages

- Sonoporation is the use of ultrasound and microbubbles to enhance therapeutic effect of existing medical agents
- Sonoporation is a bio-mechanical effect where microbubbles interact with cells
- Sonoporation can inhibit tumour growth
- Phase I clinical trial has shown sonoporation can be safe and potentially double survival in patients with pancreatic cancer (PDAC)

Pearls and Pitfalls

Pearls

- Simple and low-cost implementation using existing technology and clinical methods
- Can enhance therapeutic efficacy in preclinical and early clinical models

Pitfalls

- Can only be used if possible to visualise the lesion using ultrasound imaging
- Not optimal for treatment of multiple tumours or if there is significant metastatic spread

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Future Perspectives
- Sonoporation is at an early development stage with multiple ways of implementation
- Better understanding of what the optimal ultrasound conditions, microbubble variables, and durations are may significantly enhance the potential of sonoporation
- Very little is truly known about how the *in vivo* mechanisms work and why it is so beneficial

83.1 Background

83.1.1 Treatment of Pancreatic Cancer

When it comes to treating PDAC, it notoriously shows a very low **response to chemotherapy** due to a dense desmoplastic stroma and poor blood supply [1, 2], though perfusion is sufficient to observe significant CEUS signal [3, 4]. Despite the "curative" intent of treatment for those patients who present with surgically amenable PDAC and undergo resection followed by adjuvant systemic therapy (with or without radiation), their median overall survival is still only 15 months [5, 6].

Currently there are two major chemotherapeutic regimens for the treatment of non-resectable PDAC, a combination of Leucovorin, Fluorouracil, Irinotecan and Oxaliplatin (FOLFIRINOX), considered the first line treatment, or a combination of gemcitabine with a nanoparticle formulation of Paclitaxel (Nab-Paclitaxel), the second line treatment. These regiments only results in a median overall survival of approximately 12 months [7, 8]. For this reason, innovative strategies need to develop for effective diagnosis, drug delivery and treatment monitoring, resulting in improved outcomes for PDAC patients.

83.1.2 Sonoporation

Sonoporation uses ultrasound and ultrasound contrast agents (UCAs) to enhance the therapeutic efficacy of a given drug in a specific tissue. This is achieved by ultrasonically exciting UCAs (microbubbles) which pulsate near biological barriers (cell membrane or vascular wall). The ultrasound forces the microbubbles to rapidly expand and contract (Fig. 83.1a). This increases the permeability (Fig. 83.1b) or induces stress signalling in the cells, thereby enhance the extravasation or increasing sensitivity to external substances such as drugs and chemotherapeutics.

Taking into account that a major drawback to traditional chemotherapy is the systemic toxic side effects, especially when used in high therapeutic concentrations, sonoporation may provide an effective solution. This scenario results in greater treatment efficacy, improving quality of life and, theoretically, survival. As the

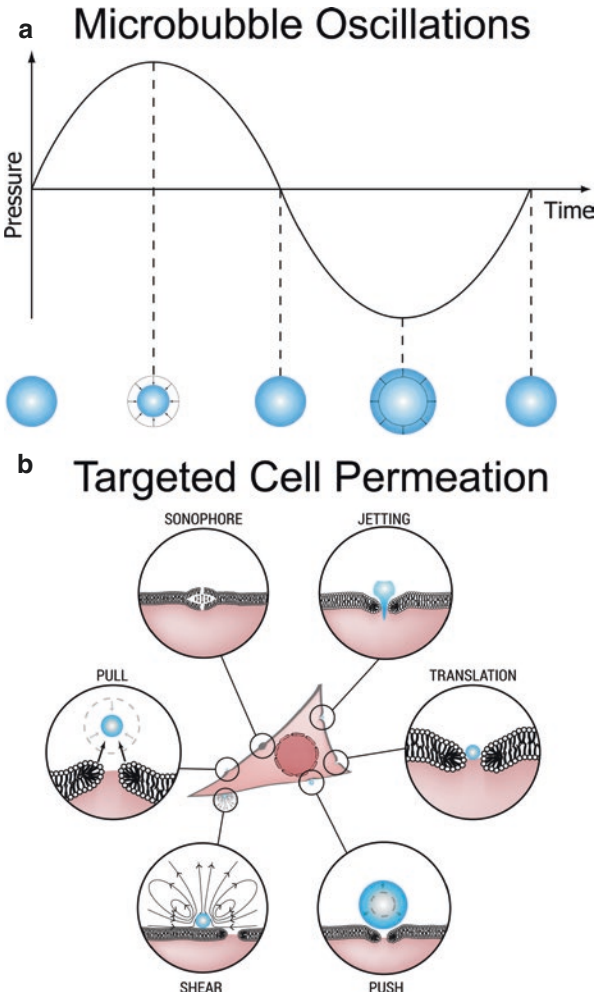

Fig. 83.1 Mechanisms of sonoporation. Ultrasound is applied to the treatment area and when the microbubbles pass through the ultrasound field the react the positive and negative acoustic pressures by contracting and expanding respectively, *i.e.*, oscillating (**Panel a**). These oscillating microbubbles interact with nearby cells and can form small holes in the cell membrane (**Panel b**). This interaction can initiate numerous other mechanisms that allow enhanced drug delivery and sensitivity

primary tumour is treated more effectively than with chemotherapy alone, there is an increased likelihood of downgrading the tumour, potentially allowing for surgical resection. As the chemotherapy remains systemic, it will still abate metastatic development.

Sonoporation, as a concept, is not new. Over the last 20 years, the field of sonoporation [9–14] has been moving towards clinical application to enhance delivery of drugs [9, 15, 16] or genetic material [10, 17–19] in cardiovascular [20, 21], hepatic [9], musculoskeletal [17, 22, 23], and neural [24] disorders.

The term sonoporation was first published in 1997 [25] and extensive research has been performed since then. A current dispute in the field is the definition and use of the term "sonoporation" as this makes the assumption that the primary mechanism behind the enhanced efficacy ultrasound and microbubble enhance therapy is

only transient pore formation in the cells [26]. Nevertheless, whilst the term has stuck, it is widely accepted that the biophysical and biochemical phenomena behind this enhanced therapeutic effect is far more complex than simple pore formation and enhanced drug delivery.

In general, the sonoporation field is split in two camps; high-intensity *vs*. low-intensity sonoporation. A majority of academic research currently focuses on the use of high-intensity ultrasound that surpasses the safe diagnostic threshold set by the FDA and IEC/EMA [27–29].

The high-intensities result in a phenomenon known as inertial cavitation (violent explosions within tissue and blood, akin to boiling) which are currently difficult to control *in vivo* [30]. This inertial cavitation can also induce significant damage to healthy tissue. During high intensity sonoporation the injected microbubbles are forces to explode/implode, damaging surrounding tissue and allowing more drugs to be delivered and forcing other biological mechanism to react to this damage. These violent mechanisms could be painted as tiny hand-grenades exploding everywhere the ultrasound and bubbles are present.

In the other camp, low intensity sonoporation focuses on using ultrasound conditions that fit under current diagnostic ultrasound imaging guidelines, allowing fast translation from lab to clinic. In this case, the aim is to preserve the bubbles and force them to interact/rub against the cells, similar to washing a dish with sponge; the soap bubbles are the microbubbles, and the ultrasound acts as the sponge.

Currently there is no evidence to suggest one method is better than the other, but efficacy and patient's safety will be determined as the field progresses into more and larger clinical trials.

83.2 Pre-Clinical Studies

Pre-clinical studies are usually the fundament needed to establish basic safety and determine if there is any potential for such a therapy. Whilst there is an abundance of pre-clinical research investigating the mechanisms of sonoporation, or the effect of sonoporation with novel drugs and various cancer types, there are still limited pre-clinical studies in relevant models with clinically relevant drugs for PDAC.

One study has shown that using SonoVue® (Bracco S.p.A., Milan, Italy) to treat PDAC in an orthotopic and metastatic model was able to significantly inhibit tumour growth when performing sonoporation in combination with Gemcitabine [16]. Specifically, after 8 weeks of treatment the tumour volume of the sonoporation group was four times smaller than that of the group treated with the drug alone (Fig. 83.2). Furthermore, the metastatic spread was also inhibited, and survival was increased.

To achieve this result, the researchers treated every 7 days using 125 mg/kg Gemcitabine injected intraperitoneally followed by 50 μL bolus injection of SonoVue® and then treated for 10 min using ultrasound. The ultrasound settings chosen were specifically to comply with existing FDA, IEC/EMA guidelines for diagnostic imaging, i.e., a mechanical index of 0.2 (diagnostic upper limit is 1.9) and a spatial-peak, temporal-average intensity of 688 mW/cm^2 (upper limit of 720 mW/cm^2).

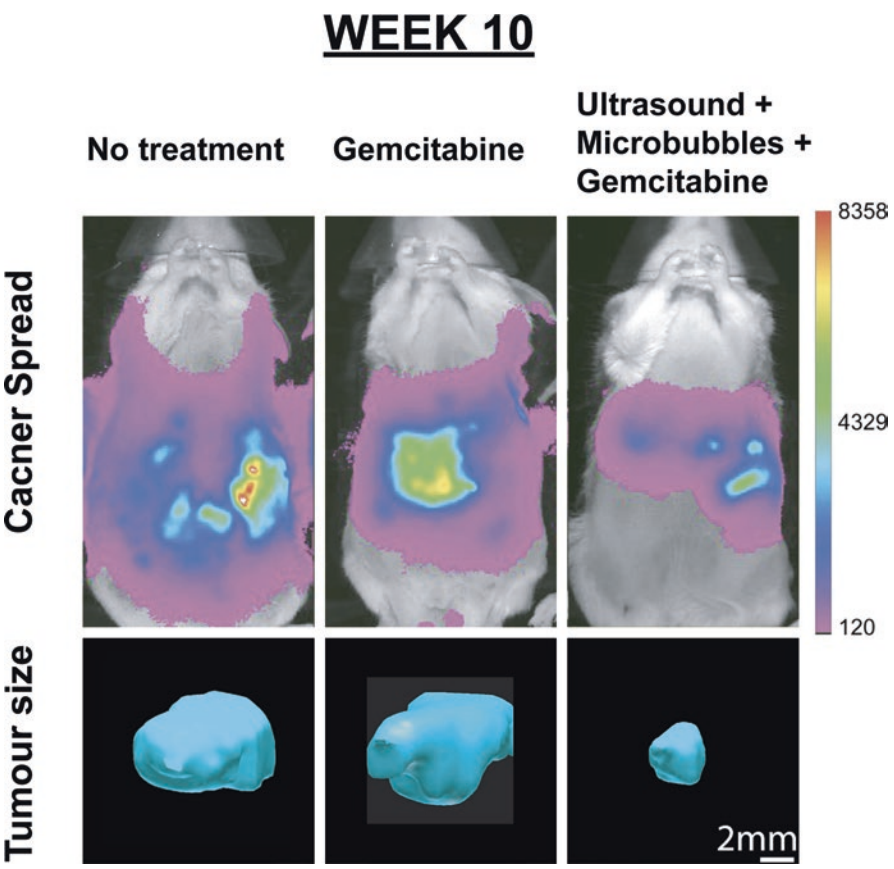

Fig. 83.2 Sonoporation in an orthotopic pancreatic cancer mouse model. Effect of sonoporation in an orthotopic pancreatic cancer mouse model after eight treatment cycles. The cancer "spread" is detected via full body bioluminescence. The primary tumour was measured using 3D ultrasound imaging. The group treated with ultrasound + microbubbles + Gemcitabine showed the least tumour spread and the smallest primary tumour

Further work has also shown that using next generation microbubbles, such as Acoustic Cluster Therapy [31] specifically designed for therapy it may be possible to even reduce the tumour volume and affect the tumour vasculature [15].

83.3 Real World Application

To date, there has only been a single complete and published Phase I clinical trial evaluating low acoustic intensity sonoporation in PDAC [4]. In this study, ten consecutive voluntary patients with inoperable pancreatic ductal adenocarcinoma were recruited. Based on CT scans before the start of treatment 30% of the patients were metastatic whereas the remainder were classified as locally advanced. A study

exploring the use sonoporation at acoustic intensities known to destroy the microbubbles also evaluated a single patient with pancreatic carcinoma [32]. This single patient showed progressive disease.

83.3.1 Treatment Protocol

All patients received the current standard of care, which at the time was gemcitabine as a monotherapy with dose scaling depending on the chemotherapy induced myelosuppression. Immediately after the end of the 30-min gemcitabine infusion, where the blood plasma level of gemcitabine was measured to be at its peak, the sonoporation procedure was initiated.

In general, the application of ultrasound is a simple procedure; the tumour is located using traditional imaging methods, and the ultrasound probe is locked into place without applying too much pressure to allow a relaxed breathing motion. The probe was positioned to minimise any ultrasound application to any other organs, e.g., stomach or intestines. In all cases the ultrasound probe was fixed and targeted at the primary tumour. An example of how a patient would be treated, and a representative US image is shown in Fig. 83.3.

SonoVue® was injected i.v. as a 0.5 mL bolus every 3.5 min followed by a 5-mL saline flush. This was repeated until the vial of SonoVue® was used up, i.e., a total of 31.5 min of ultrasound application and nine injections.

In total the duration of the treatment, including chemotherapy infusion, was just over an hour (at 61.5 min).

83.3.1.1 Choice of Microbubble Conditions

Comparing and translating drug doses from mice studies to humans is rarely an easy task. A 50-μL bolus in a mouse is approximately 2% of the total blood volume (as used in the preclinical study described earlier). This would be equivalent of injecting 100 mL of microbubbles in a human if linearly transposed from mouse to human based on blood volume. Nevertheless, blood distribution, and organ size between both species is vastly different, and the simple difference in size between the two makes it difficult to obtain a true and accurate conversion ratio.

In this study, the microbubble dose was chosen to mimic typical safe and already used clinical imaging procedures. Therefore, the tumour could be visualised accurately and continuously during therapy. This monitoring was essential since it means if the targets moves for any reason such as patient movement, or probe slipping, it can easily and rapidly be positioned to visualise and treat the tumour again.

A secondary aspect was the microbubble induced attenuation. The more bubbles in the blood, the less the ultrasound can penetrate. This means, that if the microbubble dose is too high only the portion closest to the tumour will receive enough ultrasound hence only a small portion of the tumour will be treated.

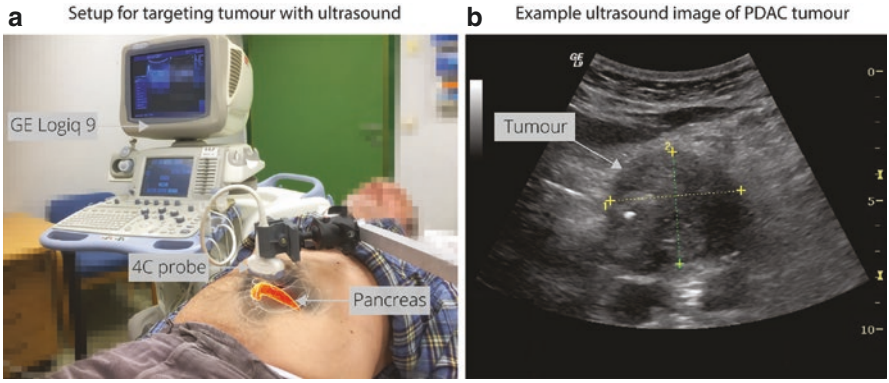

Fig. 83.3 Example of how the sonoporation treatment procedure is performed (**Panel a**) and a typical US image of a PDAC tumour (**Panel b**). (Figure modified from Dimcevski et al. [4].) Patients treated with sonoporation will typically lay down on a bed with their abdomen exposed (**Panel a**). The ultrasound probe is placed directly above the tumour and the ultrasound image is used to guide the treatment (**Panel b**). The entire tumour should be visible during the treatment period

A bolus was chosen as this followed the standard imaging procedures and it allowed transient periods of high concentrations and low concentrations of microbubbles, meaning even if the ultrasound was "blocked" from reaching deeper parts of the tumour this is only for a short period of time, hence potentially getting the benefit of transient high concentrations and low concentrations of microbubbles.

83.3.1.2 Choice of Ultrasound Conditions

The choice of ultrasound conditions was defined by the flexibility of the ultrasound system used. In this case a GE Logiq 9 (GE Healthcare, Chicago, IL, USA) combined with a 4C ultrasound probe (Fig. 83.3a).

A nonlinear contrast mode was chosen to allow visualisation of the injected microbubbles, allowing detection of a failed injection or a bad batch of microbubbles. To prevent a destruction of the microbubbles a low Mechanical Index (0.2) with a low number of cycles (4) was chosen. Increasing either would increase the destruction or dissolution speed of the microbubbles, and here the aim was to keep the microbubbles present in the circulation as long as possible. It was also attempted to maximise the number of ultrasound bursts per frame, and to increase the frame rate to maximise ultrasound exposure time.

83.4 Results

The study showed that patients treated with sonoporation in combination with gemcitabine showed no increased adverse effects, indicating that at the given conditions, sonoporation is safe and non-toxic compared to gemcitabine alone.

The treatment efficacy was compared to an inclusion criterion matched historical control cohort treated at the same hospital and department. In general, the patients treated with sonoporation were able to undergo an increased amount of treatment cycles; from 9 to 14 cycles (mean) (Fig. 83.4a), specifically, on average, a 66% increase in the amount of cycles each patient was able to undergo. This indicated that the sonoporation treated patients had an extended period of well-being. When comparing survival curves, the sonoporation treated patients had a median overall survival of 18 months *vs.* 9 months for the control group (Fig. 83.4b). Last but not least, Fig. 83.4c shows the tumour volume response from a patient that underwent sonoporation therapy. The tumours were segmented from the CT scan used to determine patient response as part of the current standard of care. A dramatic decrease in tumour volume could be observed in this patient. This patient was able to undergo optimal debulking surgery. A total of 50% of patient showed a tumour size decrease.

83.5 Current Limitations and Future Research

The field of sonoporation is still at its infancy and is far from reaching its true potential. At the current stage, research is still being performed to both fully understand the mechanisms of action and to determine which treatment parameters are optimal. Table 83.1 lists a few aspects that are yet to be solved.

Whilst *in vitro* and *in vivo* research suggests that more bubbles may be more effective as there is more interaction between the cell/blood vessels. Nevertheless, translating these microbubble conditions, and corresponding ultrasound conditions from a 1 cm deep mouse tumour to a 10 cm deep human tumour becomes a major challenge and determining a patient specific microbubble dose may be the optimal middle ground.

Another challenge is the current technology used to treat the tumours. The issue once again stems back to the initial research on mice, *vs*. transition to larger humans. The small sub 1-cm diameter tumour on mice fit within the sound field of typical single element research transducer, but human pancreatic cancer tumours are typically in the range of 2–6 cm in diameter, i.e., much larger than the slice-thickness of the diagnostic ultrasound field. Whilst the sound field maybe be less than a centimetre thick in clinical diagnostic ultrasound probes the patients breathing and internal organ movements typically allow the tumour to move throughout out the sound field. This partially mitigates the issue and allows a larger portion of the tumour to be treated but comes at the expense of accurate ultrasound dosimetry, which may have a significant impact on treatment efficacy. Hence, novel 3D/4D ultrasound probes may be a significant step forward for accurate full tumour treatment.

The clinical trial mentioned only focused on treating the primary tumour in the patients, yet a large portion of patients present with metastasis. In this first study, it took 31.5 min to treat the single tumour and then due to the pharmacokinetics, the sonoporation window was assumed to have passed. Thus, indicating that it may not be possible to treat multiple tumours using sonoporation. Nevertheless, this

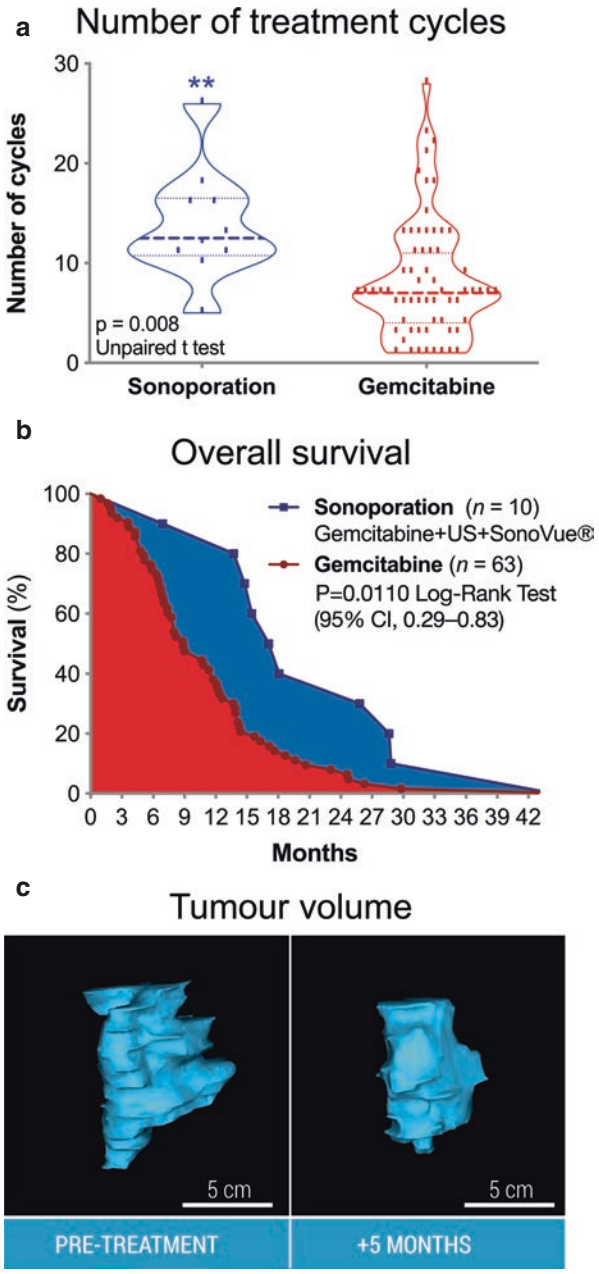

Fig. 83.4 Results of sonoporation in combination with gemcitabine to treat patients with pancreatic ductal adenocarcinoma. The patients were able to undergo an increased amount of treatment cycles (**Panel a**) indicating a longer period of well-being. The patients showed an increase in overall survival (**Panel b**). **Panel c** shows an example of the tumour volume before and after sonoporation treatment based on CT images

extensive duration was chosen due to the limited ultrasound that could be delivered. By improving the ultrasound dose, the treatment window could be further decreased. In addition, some research has indicated that the sonoporation effect happens within a few seconds of applying the ultrasound at the correct dose. What's more as the

Table 83.1 Items that still need to be explored to advance the field of ultrasound and microbubble enhanced therapy

Items that still need to be explored
What is the required minimum duration of treatment? Reducing the treatment time would mean more lesions could be treated, allowing the inclusion of metastatic diseases
What ultrasound pressures and energies are required to maximise treatment efficacy? Different microbubbles respond differently to the same ultrasound, meaning the ultrasound settings need to be adapted to the chosen bubble
Which therapeutic agents does this method work best with? In cases where the therapy is not limited by the uptake of the drug, but drug potency, sonoporation may not be of added benefit
What type of microbubbles are best? Is it worth exploring drug loaded concepts, or minor modification to existing bubbles good enough and a faster route to clinical implementation?
What type of cancers are most suitable? *In vitro* research shows different cells have different sensitivity to sonoporation, hence specific cancers may be more appropriate for sonoporation
Which model? There are no *in vitro* or animal models that mimic any cancer perfectly with a human immune system, tumour size and cellular structure. Hence more work needs to focus on the clinical evaluation and implementation of sonoporation

fields understanding of sonoporation has improved, it may be possible to perform ultrasound treatment before chemotherapeutic administration and result in the same or even improved therapeutic outcome. In summary, it may be feasible to treat tumours in a few min as long as the ultrasonic and microbubble dosimetry is correct.

A strong benefit of sonoporation is that it is predominantly a biomechanical phenomenon that enhances the therapeutic efficacy of a chosen agent. This means it should be possible to enhance the therapeutic efficacy of various therapeutic agents, both old and new. However, the mechanism of action for these therapeutic agents needs to be understood and evaluated prior to assuming sonoporation may improve its efficacy.

Last, but not least, the safety of this method needs to be thoroughly evaluated prior to assuming it is safe. With the onset of next-generation microbubbles and higher and higher power ultrasound, any combination could induce enough cellular stress or physical tissue damage.

83.6 Conclusions

Sonoporation has shown great potential in the *in vitro* and pre-clinical stage of development and is now starting to reach clinical translation. An initial clinical study has shown great promise, indicating it potential but the field is still in its infancy with many parameters still needing to be optimised to maximise its efficacy.

References

1. Provenzano PP, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21:418–29.
2. Tod J, Jenei V, Thomas G, Fine D. Tumor-stromal interactions in pancreatic cancer. Pancreatology. 2013;13(1):1–7. https://doi.org/10.1016/j.pan.2012.11.311.
3. Kotopoulis S, et al. Treatment of human pancreatic cancer using combined ultrasound, microbubbles, and gemcitabine: a clinical case study. Med Phys. 2013;40:072902.
4. Dimcevski G, et al. A human clinical trial using ultrasound and microbubbles to enhance gemcitabine treatment of inoperable pancreatic cancer. J Control Release. 2016;243:172–81.
5. Chen EL, Prinz RA. Long-term survival after pancreatic cancer treatment. Am J Surg. 2007;194:S127–30.
6. Riall TS, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma – Part 3: Update on 5-year survival. J Gastrointest Surg. 2005;9:1191–206.
7. Raoul J-L, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25. https://doi.org/10.1056/nejmoa1011923.
8. Hammel P, et al. Phase II LAPACT trial of *nab*-paclitaxel (*nab* -P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC). J Clin Oncol. 2018;36:204.
9. Castle J, et al. Ultrasound-mediated targeted drug delivery: recent success and remaining challenges. Am J Physiol Heart Circ Physiol. 2013;304:H350–7.
10. Delalande A, Kotopoulis S, Postema M, Midoux P, Pichon C. Sonoporation: mechanistic insights and ongoing challenges for gene transfer. Gene. 2013;525:191–9.
11. Postema M, Gilja OH. Ultrasound-directed drug delivery. Curr Pharm Biotechnol. 2007;8:355–61.
12. Postema M, Gilja OH. Contrast-enhanced and targeted ultrasound. World J Gastroenterol. 2011;17:28–41.
13. Escoffre J-M, Zeghimi A, Novell A, Bouakaz A. In-vivo gene delivery by sonoporation: recent progress and prospects. Curr Gene. 2013;13:2–14.
14. Lanza GM, et al. Assessing the barriers to image-guided drug delivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014;6:1–14.
15. Kotopoulis S, et al. Sonoporation with Acoustic Cluster Therapy (ACT®) induces transient tumour volume reduction in a subcutaneous xenograft model of pancreatic ductal adenocarcinoma. J Control Release. 2017;245:70–80.
16. Kotopoulis S, et al. Sonoporation-enhanced chemotherapy significantly reduces primary tumour burden in an orthotopic pancreatic cancer xenograft. Mol Imaging Biol. 2014;16:53–62.
17. Delalande A, et al. Ultrasound and microbubble-assisted gene delivery in Achilles tendons: long lasting gene expression and restoration of fibromodulin KO phenotype. J Control Release. 2011;156:223–30.
18. Carson AR, et al. Gene therapy of carcinoma using ultrasound-targeted microbubble destruction. Ultrasound Med Biol. 2011;37:393–402.
19. Tsuchiya A, et al. Efficient delivery of signal-responsive gene carriers for disease-specific gene expression via bubble liposomes and sonoporation. Colloids Surf B Biointerfaces. 2017;160:60–4.
20. Slikkerveer J, et al. Ultrasound enhanced prehospital thrombolysis using microbubbles infusion in patients with acute st elevation myocardial infarction: pilot of the sonolysis study. Ultrasound Med Biol. 2012;38:247–52.
21. Bekeredjian R, Chen S, Pan W, Grayburn PA, Shohet RV. Effects of ultrasound-targeted microbubble destruction on cardiac gene expression. Ultrasound Med Biol. 2004;30:539–43.
22. Mehier-Humbert S, Bettinger T, Yan F, Guy RH. Ultrasound-mediated gene-delivery: kinetics of plasmid internalization and gene expression. J Control Release. 2005;104:203–11.

23. Chen S, Shohet RV, Bekeredjian R, Frenkel P, Grayburn PA. Optimization of ultrasound parameters for cardiac gene delivery of adenoviral or plasmid deoxyribonucleic acid by ultrasound-targeted microbubble destruction. J Am Coll Cardiol. 2003;42:301–8.
24. Phenix CP, Togtema M, Pichardo S, Zehbe I, Curiel L. High intensity focused ultrasound technology, its scope and applications in therapy and drug delivery. J Pharm Pharm Sci. 2014;17:136–53.
25. Bao S, Thrall BD, Miller DL. Transfection of a reporter plasmid into cultured cells by sonoporation in vitro. Ultrasound Med Biol. 1997;23:953–9.
26. Snipstad S, et al. Sonopermeation to improve drug delivery to tumors: from fundamental understanding to clinical translation. Expert Opin Drug Deliv. 2018;15(12):1249–61. https://doi.org/10.1080/17425247.2018.1547279.
27. Piscaglia F, et al. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): update 2011 on non-hepatic applications. Ultraschall Med. 2012;33:33–59.
28. Barnett SB, et al. International recommendations and guidelines for the safe use of diagnostic ultrasound in medicine. Ultrasound Med Biol. 2000;26:355–66.
29. U.S. Department of Health and Human Services. Food and Drug Administration. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. 2008.
30. Rewcastle J, Gill I. High-intensity focused ultrasound for the treatment of prostate cancer. Image Guid Prostate Cancer Treat. 2014.
31. Sontum P, et al. Acoustic cluster therapy (ACT)—a novel concept for ultrasound mediated, targeted drug delivery. Int J Pharm. 2015;495:1019–27.
32. Wang Y, et al. Clinical study of ultrasound and microbubbles for enhancing chemotherapeutic sensitivity of malignant tumors in digestive system. Chin J Cancer Res. 2018;30(5):553–63. https://doi.org/10.21147/j.issn.1000-9604.2018.05.09.

Chapter 84
Best Supportive Care in Advanced Pancreatic Cancer

Anne-Laure Védie and Cindy Neuzillet

Take Home Messages

- Supportive care, by reducing symptoms, improving quality of life (QoL), allowing best treatment and decreasing side effects, holds a major place in pancreatic ductal adenocarcinoma (PDAC) management at the diagnosis and throughout the course of the disease.
- Management of common symptoms including pain, anxiety/depression, and malnutrition is crucial and requires frequent reevaluation.
- Pain management relies on analgesics with the classical WHO step-up approach, combined with neuropathic drugs and treatment of other causes abdominal discomfort (e.g. exocrine pancreatic insufficiency, constipation).
- PDAC-related malnutrition is multifactorial, involving the tumour itself, treatments and complications (e.g. infections).
- Global energetic needs are estimated at 30–35 kcal/kg/day with 1.2–1.5 g/kg/day of protein intake.
- Malnutrition, sarcopenia and cachexia have a negative impact on patient survival and QoL and are associated with increased risk of treatment complications, hospital admissions and costs.
- Nutritional support and adapted physical activity are the two main pillars of the management of sarcopenia and cachexia.

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Pearls and Pitfalls

- Supportive care is centered on the patient but should also include the family and carers.
- Malnutrition prevalence is higher in older patients and at advanced cancer stage, and frequently underestimated in obese patients.
- Malnutrition should be diagnosed and treated as early as possible, because sarcopenia and cachexia are not reversible at late stages.
- Artificial nutrition interventions are not recommended if life expectancy is shorter than 3 months.
- A sudden upsurge of pain, previously well controlled, may be a sign of disease progression, or side effects of pain killers (e.g. constipation) or pancreatic cancer (e.g. exocrine pancreatic insufficiency).

Future Perspectives

- Randomized controlled studies are needed to adequately evaluate the efficacy and determine the optimal modalities of supportive care programs (e.g. nutrition and adapted physical activity).

84.1 Introduction

Pancreatic ductal adenocarcinoma (PDAC) incidence is increasing worldwide [1]. It is expected to become the second leading cause of cancer-related death by 2030 in Europe and in the United States [2, 3]. It is the digestive tumour with the poorest prognosis, with five-year overall survival (OS) rates not exceeding 7–8% [4, 5]. Most PDAC patients have advanced disease at diagnosis (locally advanced, 30% or metastatic, 50%). Late diagnosis, due to unspecific symptoms and lack of biomarkers and screening methods for detection at early stage, together with high metastatic potential and resistance to medical therapies, are the main causes for PDAC poor prognosis [4, 6].

Beside conventional anti-tumour therapies (i.e. surgery, chemotherapy, and radiotherapy), palliative and supportive care holds a major place in PDAC management [7]. Supportive care aims at reducing symptoms due to tumour and treatment adverse effects, preventing hospital admissions, and improving health-related quality of life (HRQoL), which is a surrogate prognostic indicator for OS in PDAC [8, 9]. Supportive care should be systematically implemented in all PDAC patients, whatever the tumour stage, at the time of diagnosis and during every step of the course of the disease, in order to improve patients' general condition (*performance status*, PS) so that they can receive optimal treatment [10]. Optimal management implies avoiding both undertreatment and inappropriate end-of-life aggressiveness [11]. Best supportive care encompasses a broad spectrum of interventions from the treatment of pain, anxiety and depression, chemo(radio)therapy-related toxicities and surgery sequelae, thromboembolic disease, fatigue, malnutrition, sarcopenia

and cachexia, to psychological assistance to carers [8, 12]. These symptoms are complex and multifactorial in their origins thus their management requires a multidisciplinary therapeutic approach involving oncologists, surgeons, gastroenterologists, nutritionists and dieticians, radiologists, pain and palliative care specialists, nurses and physical activity professionals [13]. Of note, nutrition and physical activity interventions require adaptation to the specificities of PDAC setting and stage of the disease.

This chapter provides an overview of palliative and supportive care interventions in advanced PDAC, with a highlight on nutritional and physical activity management.

84.2 Non-specific Management of Common Symptoms

84.2.1 Pain

Abdominal pain is the most frequent symptom in PDAC, reported by 75% of patients at diagnosis [13]. Almost all patients with advanced PDAC suffer from pain [14]. Clinically, pancreatic pain is characterized by severe intensity, often requiring morphinic analgesics, and epigastric location with posterior irradiation. Pain in PDAC shares common pathogenesis with chronic pancreatitis pain, combining visceral (tissue destruction and inflammation, pancreatic duct obstruction) and neuropathic (perineural invasion by cancer cells, involving the celiac plexus) mechanisms [13]. Therefore, the addition of neuropathic agents (e.g. gabapentine, pregabaline, nortriptyline, duloxetine) should be systematically considered in association to classical step-up approach based on World Health Organization (WHO) pain ladder scale [15, 16]. Drug combination aims at increasing the effectiveness of the analgesic treatment by acting on different targets of nociception, while reducing overall side effects (in particular, opioid-induced pruritus, nausea, and constipation) [13]. Abdominal discomfort can also be to the consequence of pancreatic exocrine insufficiency, bile acid malabsorption, constipation, or bacterial overgrowth (Fig. 84.1). In case of uncontrolled pain despite well-conducted medical treatment, interventional techniques (i.e. endoscopic ultrasound-guided or image-guided percutaneous neurolytic celiac plexus block, or palliative radiotherapy) may be considered in selected patients [13, 15, 17].

84.2.2 Anxiety and Depression

Only few, small observational studies assessed depression or anxiety in patients with PDAC and suggested that these disorders were more prevalent in PDAC patients than in other cancer populations with similar prognosis [12, 18]. Interestingly, anxiety, but not depression, is even more common in carers than in patients (39% *vs.* 15%, and 58% *vs.* 70%, respectively) [12]. Depression has a significant impact on HRQoL and survival [19]. Questionnaires (e.g. Hospital Anxiety

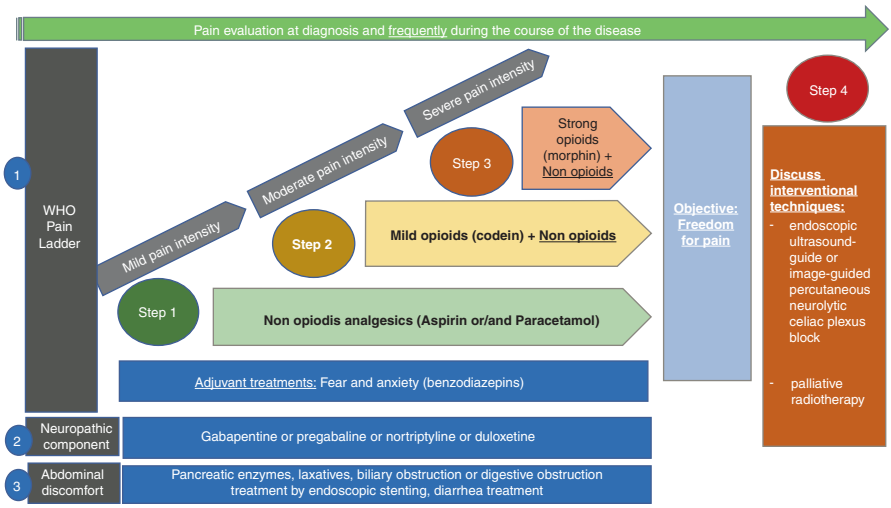

Fig. 84.1 The three pillars of the management of digestive cancer pain: WHO pain ladder, neuropathic component, abdominal discomfort

and Depression Scale [HADS] and Beck Depression Inventory [BDI]) may be useful tools for screening and evaluation of these symptoms. Anxiety-depressive disorders and psychological distress should be managed on an individual basis and relies on non-pharmacological interventions (psychotherapy, cognitivo-behavioural therapy, support groups), other symptom control (e.g. pain), and, if required, antidepressant medication [18].

84.2.3 Thromboembolic Events

Venous thromboembolic events (VTE) are the second leading cause of death in patients with cancer [20]. 20–35% of patients with PDAC (up to 60% in autopsy series) are affected by VTE during the course of the disease, making it one of the most thrombogenic tumours [13, 21]. Increased coagulability is induced by systemic inflammation and cancer cell secretion of factors that trigger the clotting cascade [22]. Blood cell count analysis (elevated leukocyte count >11,000/mm^3 and platelet count ≥350,000/mm^3 and decreased haemoglobin <10 g/dL or treatment with erythropoietin derivative), along with body mass index (BMI) ≥35 kg/m^2, have turned out to be useful in risk prediction and these four parameters have been included in the **Khorana score** to assess VTE risk in cancer patients [23, 24] (cf. Table 84.1). In patients with PDAC, the presence of one of these risk factors is sufficient to reach the high-risk threshold score of 3, at which primary thromboprophylaxis may be considered [24]. The high efficacy and feasibility of primary pharmacologic prevention of symptomatic VTE in ambulatory patients with advanced PDAC using low molecular weight heparin (LMWH) has been demonstrated in the CONKO-004 phase III study (cumulative incidence rates of

Table 84.1 Prediction score to evaluate venous thromboembolism risk: the Khorana score

Patients' characteristics	Risk score
Site of cancer	
– Very high risk (stomach, pancreas)	2
– High risk (lung, lymphoma, gynaecological, bladder, or testicular)	1
Prechemotherapy platelet count ≥350 * 10^9/L	1
Prechemotherapy haemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 * 10^9/L	1
Body mass index ≥35 kg/m^2	1

symptomatic VTE: 15.1% in the observation group and 6.4% with enoxaparin; p = 0.01) [25]. Recent guidelines recommend thromboembolic prophylaxis with LMWH or with direct oral anticoagulant in all hospitalized and ambulatory patients with locally advanced or metastatic PDAC treated with systemic anticancer therapy and who have a low risk of bleeding, thereby widening the indication spectrum of the Khorana score [26].

When the diagnosis of VTE is made in a patient with advanced PDAC, LMWH, once per day, when creatinin clearance is >30 ml/min, is recommended for the first 5–10 days of anticoagulant treatment and is preferred over vitamin K antagonists in early maintenance [26]. Direct oral anticoagulants (after 5 days of parenteral anticoagulation minimum) may be used in patients who are not at high risk of gastrointestinal bleeding [26]; they should be avoided or used with caution in PDAC patients with portal hypertension. Noticeably, the majority of trials comparing direct oral anticoagulants and LMWH have excluded patients who had upper gastrointestinal malignancy. After the occurrence of a VTE in a patient with advanced PDAC, the anticoagulation therapy should be prolonged indefinitely [26]. In the event of VTE recurrence in patients under anticoagulation with LMWH, two options may be proposed: (1) increase LMWH by 20–25%, or (2) switch to direct oral anticoagulants [26]. For the treatment of **catheter-related thrombosis**, anticoagulant is recommended for a minimum of **3 months** and as long as the catheter is in place if it is functional, not infected, and well positioned [26]. Finally, there is no consensus regarding the management of visceral thrombosis (i.e. involving portal, mesenteric or splenic veins) in PDAC [27].

84.3 Nutrition and Physical Status

84.3.1 Definitions and Pathophysiology

There is an overlap between cachexia, sarcopenia, and malnutrition [28]. Malnutrition is defined by the association of (1) a phenotypic criteria, i.e. weight loss (≥5% in 1 month or ≥10% in 6 months, or ≥10% compared to body weight before diagnosis), low BMI (≤18.5 kg/m^2) **or** reduction of muscle mass (assessed

by biphotonic absorptiometry, bioimpedance analysis, or, muscle surface area evaluated at the level of the third lumbar vertebra [L3] on abdominopelvic computed tomography) **or** function (e.g. 6-min walking test, handgrip test) and **(2)** an etiologic factor (decreased food intake, aggressive situation as cancer or decreased absorption) [29]. Cancer-related malnutrition is classified into two grades of severity, whose clinico-biological definitions (based on BMI, weight loss, and serum albumin level) take into account the age of the patient (Table 84.2). Those criteria have been recently updated in new French guidelines [30].

Overall, **malnutrition** is present in **40% of patients** with cancer, whatever the primary tumour location and stage [31]. It is more frequent in older patients and at advanced cancer stages, and it is frequently underestimated, especially in obese patients [32]. Among cancers of the digestive tract, malnutrition prevalence is particularly high in patients with PDAC, reaching 70% [31, 33]. Pancreatic cancer related malnutrition is multifactorial, involving the tumour itself (anorexia, digestive stenosis, cholestasis and pancreatic exocrine insufficiency, diabetes mellitus, systemic inflammation, and hypercatabolism), treatments (chemotherapy and radiotherapy adverse effects and surgery sequelae) and complications (e.g. infections) (Fig. 84.2). These three combined drivers yield increased energetic and protein expenditures together with decreased oral intake and physical activity [31, 34, 35].

Sarcopenia is defined by the reduction of muscle mass, assessed using body-composition tools as described above. It has been initially described in older patients and secondary extended to muscle loss related to cancer [28]. Muscle proteolysis is an early event in PDAC carcinogenesis; it induces an important efflux of muscle amino acids, which boosts tumour progression and is detectable in blood samples collected 2–5 years before PDAC diagnosis [31, 36]. In addition, skeletal muscle insulin resistance is a hallmark of PDAC [28]. Overall, metabolic changes and secreted "atrophying" inflammatory cytokines (e.g. transforming growth factor β [TGF-β]) alter cell signalling and mitochondrial functioning in muscle fibers and result in imbalance between muscle protein synthesis and degradation, leading to sarcopenia [37, 38].

Cachexia is defined by loss of muscle function or mass associated or not with loss of fat mass and driven by inflammatory syndrome [34, 35, 39]. PDAC is prototypical of cancer-induced inflammation and hypercatabolism. Three phases of cachexia are classically described: (1) pre-cachexia, (2) cachexia, and (3) refractory cachexia [39]. High levels of inflammatory cytokines (e.g. interleukin-6 [IL-6] and its surrogate CRP) and imbalanced peripheral blood mononuclear cells (i.e. high neutrophil-to-lymphocyte ratio) are observed in PDAC patients and correlate with reduced survival [40].

Malnutrition, sarcopenia and cachexia have a significant negative impact on HRQoL and OS, and are associated with increased rates of post-operative complications, chemotherapy and radiotherapy toxicities, and infections, resulting in more frequent and longer hospital stays and higher costs [28, 41–43]. Moreover, they are associated with undertreatment, delay in therapy initiation, and toxicity-related dose reductions, leading to suboptimal treatment dose-intensity and thereby representing a lack of opportunity for patients [44].

Table 84.2 Definitions of malnutrition, severe malnutrition, and cachexia

Definition of malnutrition: ONE etiologic criteria AND ONE phenotypic criteria	Etiologic criteria	Phenotypic criteria	
	• Weight loss ≥5% of BW in 1 month • Weight loss ≥10% of BW in 6 months • Or ≥10% compared to weight before disease • BMI <18,5 kg/m^2 • Reduction in muscle mass or function	• Decreased oral intake ≥50% for more than 1 week or any reduction of food intake for more than 2 weeks compared to usual food intakes or proteino-energetics needs • Decreased absorption • Protein hypercatabolism with or without inflammatory syndrome) (e.g. cancer, infection)	
Age	**Malnutrition**	**Severe malnutrition**	**Cachexia**
<70	• 17 < BMI < 18,5 kg/m^2 • Weight loss ≥5% of BW in 1 month • Weight loss ≥10% of BW in 6 months • 30 < Albumin < 35 g/L	• BMI ≤ 17 kg/m^2 • Weight loss ≥10% of BW in 1 month • Weight loss ≥15% of BW in 6 months • Albumin ≤30 g/L	• Weight loss >5% over the past 6 months (in absence of simple starvation) • BMI < 20 kg/m^2 and any degree of weight loss >2% • Muscle atrophy (i.e., reduced muscle mass) and any degree of weight loss >2%
≥ 70	• BMI < 21 kg/m^2 • Weight loss ≥5% of BW in 1 month • Weight loss ≥10% of BW in 6 months • Albumin <35 g/L • MNA < 17	• BMI < 18 kg/m^2 • Weight loss ≥10% of BW in 1 month • Weight loss ≥15% of BW in 6 months • Albumin <30 g/L	

Note: 1 criteria is sufficient
BMI body mass index, *BW* body weight, *MNA* Mini-Nutritional Assessment

At refractory stage, these syndromes cannot be reversed by conventional nutritional support, highlighting the importance of early diagnosis and multidisciplinary therapeutic intervention, combining nutrition and adapted physical activity, as well as relief of biliary and digestive obstructions, insulin and enzyme replacement therapy, and prevention and symptomatic treatment of surgical complications and chemotherapy/radiotherapy toxicities [29, 34, 35, 39].

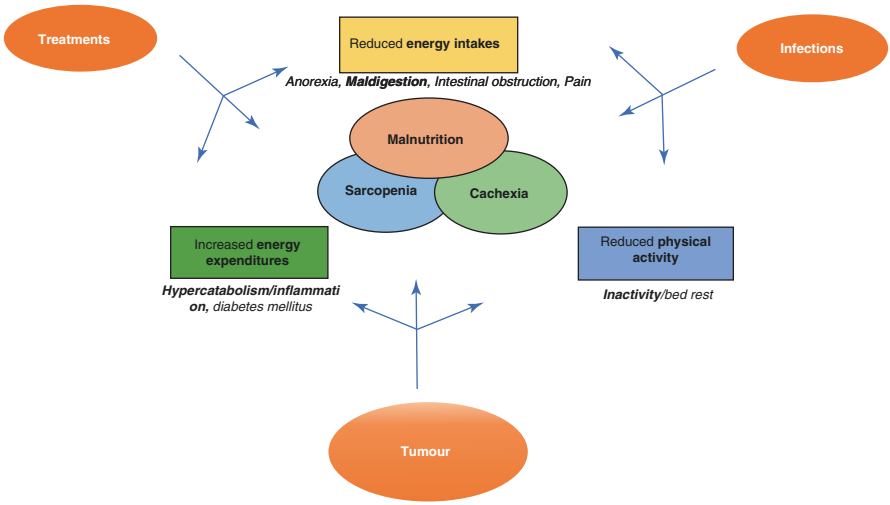

Fig. 84.2 Summary of main drivers of malnutrition, sarcopenia and cachexia in pancreatic ductal adenocarcinoma (PDAC)

84.3.2 Nutrition Care in Patients with Advanced PDAC

Nutritional status should be assessed from diagnosis using clinical and biological parameters (BMI, weight loss, food intakes, and serum albumin level) and re-evaluated regularly during the course of the disease [29, 30]. Questionnaires (e.g. Malnutrition Universal Screening Tool, Mini Nutritional Assessment, Glasgow Prognostic Score) are less widely used in routine clinical practice but are applied in clinical trials. Dietician or nutritionist expertise to estimate calories and energy intakes and needs is highly valuable [29, 30].

Global proteino-energetic needs are estimated at almost 20–25 kcal/kg/jour in bedridden patients and 30–35 kcal/kg/day in ambulatory patients with 1.2–1.5 g/kg/day of proteins [29]. In comparison, global protein-energetic needs in an healthy adult is lower but is very different according to sex, age and activity and can be estimate with Harris and Benedict equation. Vitamin (A, D, E, B1, B6) and oligoelements deficiencies are not screened routinely but have to be screened and treated in case of severe malnutrition or short bowel syndrome. There is no need to systematic supplementation in vitamins and oligoelements except in case of parenteral nutrition where poly-vitamins and poly-oligoelements have to be added to hydration.

Nutrition counselling should be provided to all patients. It includes encouraging good oral hygiene practices to prevent mucositis or fungal mouth infection during chemotherapy, adequate fluid intake (by example: 1.5 L of water a day), fractioned alimentation with multiple small meals to stimulate appetite, and preferring cold food to avoid nausea caused by cooking smells [29].

Oral nutritional supplements, rich in proteins and calories, are routinely proposed when oral intakes are insufficient to cover needs (visual analog scale ≤7) and in case of significant weight loss even if BMI and/or albumin are normal [29]. Different forms of oral nutritional supplements exist and have to be proposed to the patients (as soup, protein cake, powdered oral nutritional supplements, ready-made milk-based 'sip feeds', semi-solid or pudding-type oral nutritional supplements and juice-style 'sip feeds'). The oral nutritional supplements, kept in the fridge, and preferentially ate chilled, have to be taken between or after the meal to avoid them to replace the normal food.

Artificial nutrition is indicated when nutrient intakes remains inadequate and less than 50% of total energy needs. Enteral route should be preferred to parenteral nutrition whenever the digestive tract is functional [29]. Nasogastric tubes can be used for up to 4–6 weeks and should be preferred to percutaneous gastrostomy in metastatic disease [29].

Home parenteral nutrition has to be considered only if enteral nutrition is not an option due to bowel obstruction, radiation enteritis, severe mucositis, or intestinal failure, in the absence of symptomatic cardiac insufficiency or decompensated diabetes mellitus [29].

Artificial nutrition interventions should be considered when the vital prognosis is threatened by nutritional status rather than by neoplastic disease and are not recommended if life expectancy is shorter than 3 months [29]. Therefore, enteral or parenteral nutrition should not be prescribed in near end-of-life setting.

84.3.3 Other Measures for Nutritional Optimization

Endoscopic biliary and/or duodenal stenting should be preferred over surgery in symptomatic patients. Metal stents are preferred but plastic stents can be considered when patient life expectancy is very short (<3 months) [45].

Ascites is a frequent complication of PDAC and may be secondary to peritoneal carcinomatosis and/or severe malnutrition [46, 47]. Regular paracentesis of compressing ascites may be required to facilitate oral food and fluid intakes, alleviate pain, and improve respiratory function. Enteral nutrition is often challenging in case of ascites. In the absence of bowel obstruction, enteral nutrition should be started carefully to evaluate tolerance, and in case of failure, parenteral nutrition may be proposed but should also be initiated progressively not to increase ascites.

Pancreatic exocrine insufficiency is estimated to affect more than 50% of patients with advanced PDAC [13]. Exocrine insufficiency may present with symptoms (fatty diarrhea, flatulence, and dyspeptic symptoms) or be subclinical. Some guidelines (NICE) recommend offering pancreatic enzymes to all patients with unresectable PDAC [48]. Otherwise, replacement therapy using at least 50,000 IU of enteric-coated pancreatin with each meal should be started promptly once exocrine insufficiency is diagnosed or suspected [49].

Endocrine insufficiency (type IIIc diabetes [50], i.e. paraneoplastic or secondary to ductal obstruction with upstream pancreatic atrophy) may also develop and be decompensated by nutritional support (particularly parenteral nutrition) or steroids, requiring anti-diabetic agents. In advanced PDAC, glycaemic objectives should be less constraining, and priority has to be given to increase oral intakes whatever the glucid percentage. Metformin might be preferred as first-line therapy for mild hyperglycaemia, and insulin considered as second-line treatment [50].

Anorexia is frequently multifactorial in cancer (involving pain, gastroparesia, early satiety, gastrointestinal obstruction, constipation, dysgueusia, mucositis, nausea, depression, and hypothyroidism) and is an important component of cachexia [34, 35]. Several drugs (e.g. ghrelin mimetics, neuroleptic drugs, progresterone analogues, corticosteroids, canabinoids and anabolic hormones) have been tested to increase appetite and food intakes, but none of them has been properly clinically validated and they cannot be recommended in PDAC patients [51, 52].

84.3.4 Physical Activity in Advanced PDAC Cancer

Physical status has to be evaluated at the time of PDAC diagnosis and should be regularly reassessed during the course of the disease, using body composition tools and strength and aerobic functional tests.

There is accumulating evidence that physical activity, by reducing disease- or treatment-related symptoms (fatigue, anxiety/depression, pain) and improving physical fitness and muscle function, is beneficial for cancer patients during and after treatment [53–55].

Cancer-related fatigue is multifactorial (due to the disease itself, bed rest, treatments) and has a major impact on patient HRQoL [55]. Deconditioning, i.e. loss of physical (cardiorespiratory function and muscle strength) and psychological fitness caused by reduced physical activity, is one of the main causes of cancer-related fatigue [9]. Bed rest is deleterious to cancer patients, by accelerating the loss of muscle mass and function and aerobic capacity, while physical exercise is the best way to reduce deconditioning and fatigue. Several studies have reported a 30%-decrease in cancer-related fatigue and potential benefit on HRQoL with physical activity practice, even in advanced-stage cancer [54, 55]. In contrast, no specific drug has shown efficacy for the treatment of fatigue in palliative care patients [56, 57].

In addition, physical exercise may also induce anti-tumour effects, through several mechanisms including reduction of insulin resistance and inflammatory factor secretion, and modulation of tumour signaling pathways [58].

Implementation of **adapted physical activity** (APA) in cancer patients implies a multidisciplinary collaboration between the cancer-care medical team and an APA

professional [59, 60]. The APA program should be individualized for each patient according to the person characteristics (physical fitness, exercise type preferences, psychological functions, and expectations), the cancer type and stage and the social environment. A combined aerobic exercise and resistance-training program is hypothesized to be the most efficient way to improve physical fitness and decrease fatigue and therefore should be favored [59, 60]. Patient adherence to the APA program is crucial for its efficacy. Performing exercise in groups of patients having similar physical capabilities and under the supervision of an APA professional trainer whenever possible is hypothesized to be the best way to ensure patient motivation. Little is known about the optimal duration of exercise interventions and no specific recommendation from evidence-based guidelines exists [53]. The APA program also requires nutrition specialist involvement to balance energy intake with energy expenditure. Of note, cancer patients have often significantly increased basal resting energy expenditure with spontaneously reduced physical activity level compared with healthy individuals [61].

Exercise interventions in cancer patients have been demonstrated to be safe and feasible both in the advanced setting and in the adjuvant setting following surgery [53, 55, 62–64]. However, randomized controlled studies are warranted to adequately evaluate the efficacy and determine the optimal modalities of APA programs (e.g. mode, intensity, frequency, duration, timing) in each cancer type. Prospective data about APA interventions specifically in PDAC patients are limited [42, 62, 63]. Patients with advanced PDAC are strongly affected by fatigue, and are thus likely to benefit from an exercise intervention [65]. However, an exercise intervention may appear challenging due to multiple PDAC-related symptoms such as fatigue, depression, pain, and malnutrition. A multicenter randomized study is ongoing in France to prospectively evaluate the efficacy of APA on HRQoL in patients with advanced PDAC (APACaP phase III trial, NCT02184663) [66]. Overall, APA combined with nutritional intervention appears as a promising non-pharmacological strategy to improve HRQoL in PDAC patients.

84.4 Conclusion

Supportive care is inseparable from anti-tumour treatments in patients with PDAC, to improve their tolerance and ensure the best conditions for their efficacy. PDAC patients experience numerous symptoms (pain, anxiety/depression, fatigue, malnutrition) of multifactorial origin, severely impacting their daily life. These symptoms require a global approach, involving joint action and complementary expertise from multidisciplinary cancer care team (Fig. 84.3). Nutritional support and adhesion to active behaviour are the two pillars of best supportive care. Future improvements in PDAC management and survival and HRQoL benefits may come from progress in supportive care as much as anti-tumour therapies.

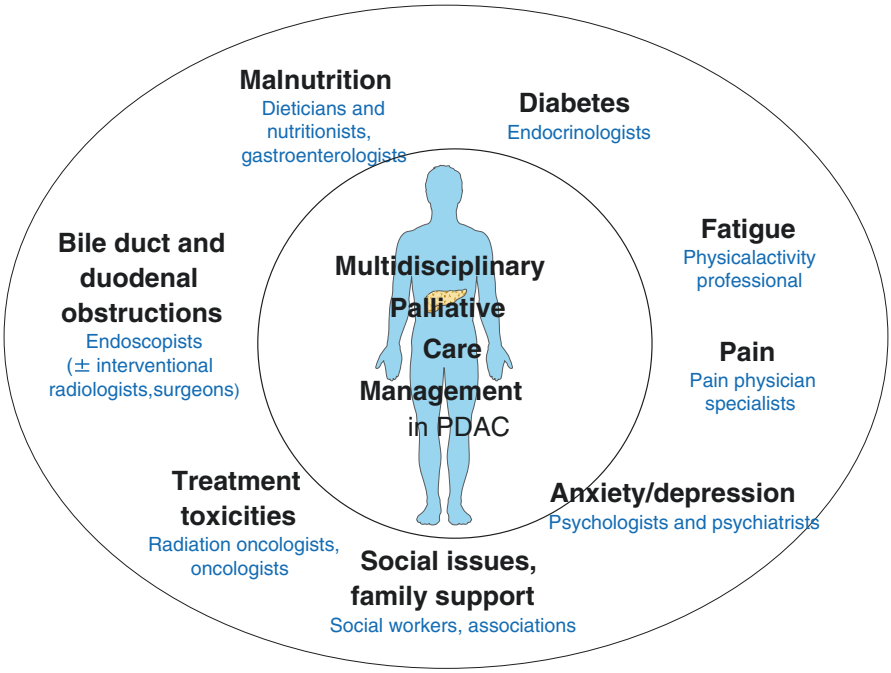

Fig. 84.3 Multidisciplinary best supportive care management in cancer patients

Competing Interest A.L.V.: none. C.N.: national coordinator of the APACaP trial.

References

1. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10–27.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
3. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol Stockh Swed. 2016;55(9–10):1158–60.
4. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, et al. Pancreatic cancer. Nat Rev Dis Primer. 2016;2:16022.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
6. Neuzillet C, Tijeras-Raballand A, Bourget P, Cros J, Couvelard A, Sauvanet A, et al. State of the art and future directions of pancreatic ductal adenocarcinoma therapy. Pharmacol Ther. 2015;155:80–104.
7. Védie A-L, Neuzillet C. Pancreatic cancer: best supportive care. Presse Medicale Paris Fr 1983. 2019;48(3 Pt 2):e175–85.
8. Bauer MR, Bright EE, MacDonald JJ, Cleary EH, Hines OJ, Stanton AL. Quality of life in patients with pancreatic cancer and their caregivers: a systematic review. Pancreas. 2018;47(4):368–75.
9. Diouf M, Filleron T, Pointet A-L, Dupont-Gossard A-C, Malka D, Artru P, et al. Prognostic value of health-related quality of life in patients with metastatic pancreatic adenocarci-

noma: a random forest methodology. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2016;25(7):1713–23.
10. Maltoni M, Scarpi E, Dall'Agata M, Zagonel V, Bertè R, Ferrari D, et al. Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial. Eur J Cancer Oxf Engl 1990. 2016;65:61–8.
11. Jang RW, Krzyzanowska MK, Zimmermann C, Taback N, Alibhai SMH. Palliative care and the aggressiveness of end-of-life care in patients with advanced pancreatic cancer. J Natl Cancer Inst. 2015;107(3)
12. Janda M, Neale RE, Klein K, O'Connell DL, Gooden H, Goldstein D, et al. Anxiety, depression and quality of life in people with pancreatic cancer and their carers. Pancreatology. 2017;17(2):321–7.
13. Laquente B, Calsina-Berna A, Carmona-Bayonas A, Jiménez-Fonseca P, Peiró I, Carrato A. Supportive care in pancreatic ductal adenocarcinoma. Clin Transl Oncol. 2017;19(11):1293–302.
14. Drewes AM, Campbell CM, Ceyhan GO, Delhaye M, Garg PK, van Goor H, et al. Pain in pancreatic ductal adenocarcinoma: a multidisciplinary, international guideline for optimized management. Pancreatology. 2018;18(4):446–57.
15. Sohal DPS, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34(23):2784–96.
16. Koulouris AI, Banim P, Hart AR. Pain in patients with pancreatic cancer: prevalence, mechanisms, management and future developments. Dig Dis Sci. 2017;62(4):861–70.
17. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–68.
18. Akizuki N, Shimizu K, Asai M, Nakano T, Okusaka T, Shimada K, et al. Prevalence and predictive factors of depression and anxiety in patients with pancreatic cancer: a longitudinal study. Jpn J Clin Oncol. 2016;46(1):71–7.
19. Skelton WP, Parekh H, Starr JS, Trevino J, Cioffi J, Hughes S, et al. Clinical factors as a component of the personalized treatment approach to advanced pancreatic cancer: a systematic literature review. J Gastrointest Cancer. 2018;49(1):1–8.
20. Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khorana AA, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2016;17(10):e452–66.
21. Muñoz Martín AJ, García Alfonso P, Rupérez Blanco AB, Pérez Ramírez S, Blanco Codesido M, Martín Jiménez M. Incidence of venous thromboembolism (VTE) in ambulatory pancreatic cancer patients receiving chemotherapy and analysis of Khorana's predictive model. Clin Transl Oncol. 2014;16(10):927–30.
22. Faille D, Bourrienne M-C, de Raucourt E, de Chaisemartin L, Granger V, Lacroix R, et al. Biomarkers for the risk of thrombosis in pancreatic adenocarcinoma are related to cancer process. Oncotarget. 2018;9(41):26453–65.
23. Pabinger I, Thaler J, Ay C. Biomarkers for prediction of venous thromboembolism in cancer. Blood. 2013;122(12):2011–8.
24. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902–7.
25. Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. J Clin Oncol. 2015;33(18):2028–34.
26. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2019;20(10):e566–81.
27. Hicks AM, DeRosa A, Raj M, Do R, Yu KH, Lowery MA, et al. Visceral thromboses in pancreas adenocarcinoma: systematic review. Clin Colorectal Cancer. 2018;17(2):e207–16.

28. Hilmi M, Jouinot A, Burns R, Pigneur F, Mounier R, Gondin J, et al. Body composition and sarcopenia: the next-generation of personalized oncology and pharmacology? Pharmacol Ther. 2019;196:135–59.
29. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr Edinb Scotl. 2017;36(1):11–48.
30. https://www.has-sante.fr/upload/docs/application/pdf/2019-11/reco277_recommandations_rbp_denutrition_cd_2019_11_13_v0.pdf.
31. Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. JPEN J Parenter Enteral Nutr. 2014;38(2):196–204.
32. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629–35.
33. Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. Oncotarget. 2017;8(45):79884–96.
34. Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes Dev. 2016;30(5):489–501.
35. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90–9.
36. Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 2014;20(10):1193–8.
37. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. 2014;14(11):754–62.
38. VanderVeen BN, Fix DK, Carson JA. Disrupted skeletal muscle mitochondrial dynamics, mitophagy, and biogenesis during cancer cachexia: a role for inflammation. Oxidative Med Cell Longev. 2017;2017:3292087.
39. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489–95.
40. Hasegawa S, Eguchi H, Tomokuni A, Tomimaru Y, Asaoka T, Wada H, et al. Pre-treatment neutrophil to lymphocyte ratio as a predictive marker for pathological response to preoperative chemoradiotherapy in pancreatic cancer. Oncol Lett. 2016;11(2):1560–6.
41. EMC F, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. JAMA Oncol. 2017;3(12):e172319.
42. Hua H, Xu X, Tang Y, Ren Z, Xu Q, Chen L. Effect of sarcopenia on clinical outcomes following digestive carcinoma surgery: a meta-analysis. Support Care Cancer. 2019;27(7):2385–94.
43. Renfro LA, Loupakis F, Adams RA, Seymour MT, Heinemann V, Schmoll H-J, et al. Body mass index is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database. J Clin Oncol. 2016;34(2):144–50.
44. Klute KA, Brouwer J, Jhawer M, Sachs H, Gangadin A, Ocean A, et al. Chemotherapy dose intensity predicted by baseline nutrition assessment in gastrointestinal malignancies: a multicentre analysis. Eur J Cancer Oxf Engl 1990. 2016;63:189–200.
45. Neuzillet C, Gaujoux S, Williet N, Bachet J-B, Bauguion L, Colson Durand L, et al. Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC). Dig Liver Dis. 2018;50(12):1257–71.
46. Hicks AM, Chou J, Capanu M, Lowery MA, Yu KH, O'Reilly EM. Pancreas adenocarcinoma: ascites, clinical manifestations, and management implications. Clin Colorectal Cancer. 2016;15(4):360–8.
47. Takahara N, Isayama H, Nakai Y, Sasaki T, Saito K, Hamada T, et al. Pancreatic cancer with malignant ascites: clinical features and outcomes. Pancreas. 2015;44(3):380–5.
48. https://www.nice.org.uk/guidance/ng85/chapter/Recommendations#nutritional-management.

49. Lindkvist B, Phillips ME, Domínguez-Muñoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: prevalence and diagnostic use. Pancreatology. 2015;15(6):589–97.
50. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1(3):226–37.
51. Ruiz-García V, López-Briz E, Carbonell-Sanchis R, Bort-Martí S, Gonzálvez-Perales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. J Cachexia Sarcopenia Muscle. 2018;9(3):444–52.
52. Mücke M, Weier M, Carter C, Copeland J, Degenhardt L, Cuhls H, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexia Sarcopenia Muscle. 2018;9(2):220–34.
53. Buffart LM, Galvão DA, Brug J, Chinapaw MJM, Newton RU. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treat Rev. 2014;40(2):327–40.
54. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev. 2012;(8):CD007566.
55. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012;11:CD006145.
56. Mücke M, Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2015;(5):CD006788.
57. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 2017;3(7):961–8.
58. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: a critical systematic review of in vivo preclinical data. Cancer Res. 2016;76(14):4032–50.
59. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243–74.
60. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. J Support Oncol. 2012;10(5):171–7.
61. Cao D, Wu G, Zhang B, Quan Y, Wei J, Jin H, et al. Resting energy expenditure and body composition in patients with newly detected cancer. Clin Nutr Edinb Scotl. 2010;29(1):72–7.
62. Wiskemann J, Clauss D, Tjaden C, Hackert T, Schneider L, Ulrich CM, et al. Progressive resistance training to impact physical fitness and body weight in pancreatic cancer patients: a randomized controlled trial. Pancreas. 2019;48(2):257–66.
63. Ngo-Huang A, Parker NH, Wang X, Petzel MQB, Fogelman D, Schadler KL, et al. Home-based exercise during preoperative therapy for pancreatic cancer. Langenbecks Arch Surg. 2017;402(8):1175–85.
64. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(5):778–88.
65. Buffart LM, Sweegers MG, May AM, Chinapaw MJ, van Vulpen JK, Newton RU, et al. Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. J Natl Cancer Inst. 2018;110(11):1190–200.
66. Neuzillet C, Vergnault M, Bonnetain F, Hammel P. Rationale and design of the adapted physical activity in advanced pancreatic cancer patients (APACaP) GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) trial: study protocol for a randomized controlled trial. Trials. 2015;16:454.

Correction to: Palliative Endoscopic Therapy in Pancreatic Cancer

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Correction to: Chapter 79 in: K. Søreide, S. Stättner (eds.), *Textbook of Pancreatic Cancer*, https://doi.org/10.1007/978-3-030-53786-9_79

Chapter 79 was inadvertently published with the following:

- Figure 79.2's legend was incomplete; this has been updated and the Figure 79.2's legend should be read as:
  Fig. 79.2 Illustration of endoscopic palliation in pancreatic cancer. (**a**) Classic biliary SEMS. (**b**) EUS-BD via hepatogastrostomy. (**c**) Intraductal radiofrequency ablation. (**d**) EUS guided celiac plexus intervention. (**e**) Duodenal stent. (**f**) EUS guided gastro-enterostomy with indwelling LAMS
- Figure 79.3 has been updated; the complete figure could be seen below:

The updated version of the chapter can be found at https://doi.org/10.1007/978-3-030-53786-9_79

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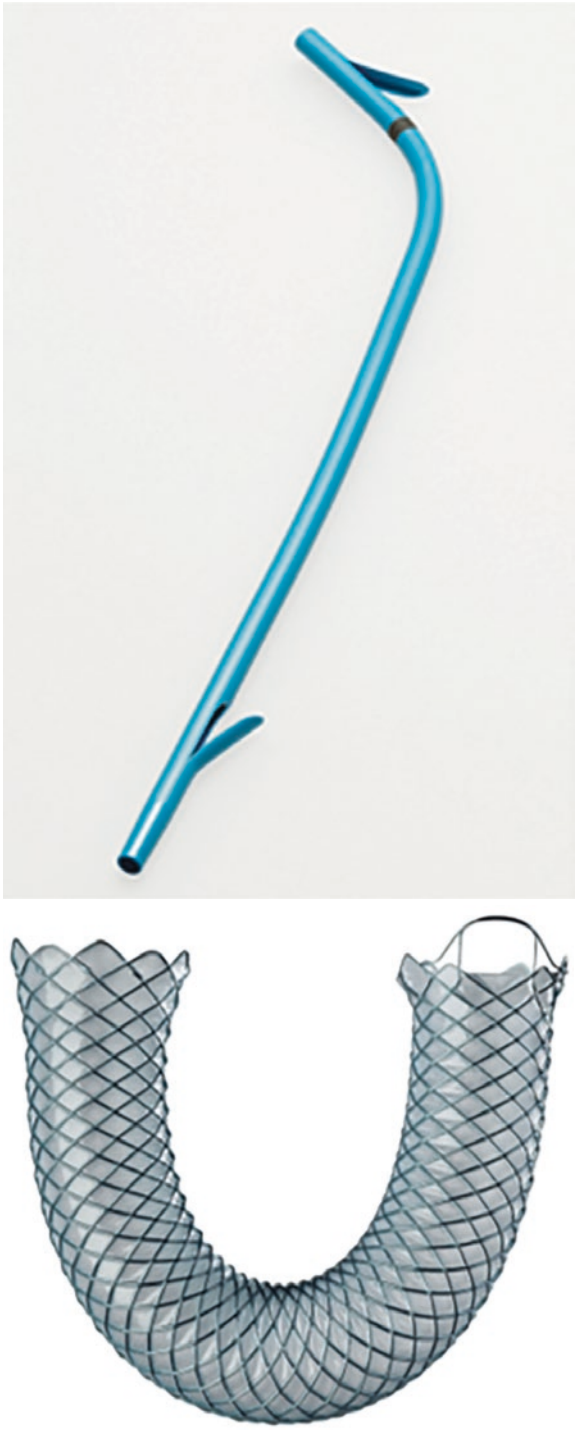

Fig. 79.3 Photograph of a biliary plastic stent (above) and fully covered biliary SEMS (below). (Material provided courtesy of Boston Scientific. Copyright 2019 © Boston Scientific Corporation or its affiliates. All rights reserved)

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