Pancreatic Cancer: A Multidisciplinary Approach

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Springer

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ISBN 978-3-031-05723-6 ISBN 978-3-031-05724-3 (eBook)
https://doi.org/10.1007/978-3-031-05724-3

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Foreword: The Evolution of Pancreatic Cancer Care

I saw my first CT scan of a patient with pancreas cancer in 1981; I was a second-year medical student on my first surgical rotation. Body CT scans had entered widespread clinical practice about 1980, the year I started medical school. I stood together with the surgery team in a dark room, facing a row of films on a rotator—a series of small, grainy images. The radiologist pointed out the organs, which appeared as vaguely identifiable blobs of varying shades of gray—the liver, the stomach, the spleen—and *there*, the pancreas, and *there*, the cancer. It was a revelation, but I had no idea at the time how much during my professional lifetime not only imaging but also so many aspects of care of patients with pancreatic cancer would improve. Of course, despite those advances, we still have a very long way to go to substantively improve outcomes and quality of life for most patients with this still far too deadly disease.

During my early medical training, surgical care of pancreas cancer patients was primitive. This was before high-quality imaging; before clinical use of CA19-9; before endoscopy, EUS, FNA, preoperative tissue diagnosis, endobiliary stents, or diagnostic laparoscopy. This was our experience: evaluate a jaundiced patient, consider doing a poorly informative imaging study (CT or an angiogram), do a laparotomy a day or so later, find metastatic disease in most patients. Close and talk to their family. Occasionally you would encounter a patient without metastases, and you would mobilize the duodenum and head of the pancreas, put your hand behind the pancreatic head and try to feel for a plane between the tumor and the SMA. You would then proceed with the operation, hope the vein was free and that your impression of SMA interface had been accurate. If you were very lucky and surgery went well, you prayed for no leak, because there was no interventional radiology. Postop evaluation was primarily based on clinical examination, and if the drain you placed in the operating room did not work, the only way to drain a significant leak was to go back to the operating room.

As a fellow and subsequently as a faculty member at MD Anderson I was very fortunate to be introduced to and then became a member of a tremendous multidisciplinary pancreas program. I had the chance to experience and eventually contribute to an organized, coordinated TEAM that challenged each other to rethink and investigate the disease, and reevaluate our treatment strategies and treatment sequencing; in doing so I am proud to be able to say that we helped improve care for patients with pancreatic cancer.

Of course, we did not do this in a vacuum, as a single program or institution. Many advances were made elsewhere, including early on that pancreatic surgery could be performed safely at high volumes by experienced teams, and more recently proof through randomized trials that adjuvant systemic therapy for patients with surgically resected pancreatic cancer could improve survival.

Now 3 decades after I first arrived at MD Anderson, the approaches and techniques that were developed here and other places have been widely and successfully adopted, implemented, and extended. One of the fundamentally important lessons of my career has been: you can teach a medical student, a resident, a fellow, and a surgical partner to do things as well as you, and often they will find ways to do to them even better. Those from my generation accomplished some fundamental things: we significantly reduced the overall risk and morbidity of pancreatic surgery; we are much better at choosing for operation those we are more likely to help; our patients are living incrementally longer and doing better with the time they have.

Of course there is so much more to be done and that is already being done—as described by my colleagues in the chapters that follow: defining the molecular mechanisms that drive pancreatic cancer development, progression, and response to therapy including through identification of clinically important tumor biomarkers, liquid biopsy technologies and imaging-based biomarkers; better strategies for early detection and prevention of pancreatic cancer; development of novel approaches to systemic, targeted and immune-based therapies including exploitation of the patient and tumor microbiome; intelligent treatment sequencing and more precise implementation of radiation therapy; sophisticated approaches in diagnostic and interventional endoscopy; improved management of challenging patient categories, including borderline resectable and locally advanced disease; advances in surgical techniques, including minimally invasive and robotic surgery, and extended operative approaches including vascular resection and reconstruction; new approaches to palliation and improvements in quality of life through evaluation and intervention, including advances in nutrition, pain management, and integrative medicine. The future of pancreatic cancer care is being written, and the outline is contained in these chapters.

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Jeffrey E. Lee

Preface

Pancreatic cancer is a dreadful disease with an increasing impact on cancer-related mortality worldwide. This disease is the unfortunate exception to the general trend of improvement in cancer-related mortality. Pancreatic cancer is projected to become the second leading cause of cancer-related deaths worldwide by 2030. There is a significant need for better treatment options to improve the survival and quality of life of pancreatic cancer patients.

In the last decade, management of pancreatic cancer has shifted towards a multidisciplinary approach with encouraging results. There have been several recent advances, from screening high-risk cohorts to emerging precision medicine paradigms, as well as recently reported practice-changing data for surgically resected patients.

This book provides a comprehensive, state-of-the-art review of this field and will serve as a valuable resource for physicians and researchers with an interest in pancreatic cancer. The book describes data about risk factors and genetic predisposition for pancreatic cancer and highlights current screening strategies and preliminary results. The diagnosis and staging of pancreatic cancer is reviewed, with focus on imaging evaluations, laparoscopy, endoscopic ultrasound-guided biopsies, and biomarkers. For locally advanced and metastatic disease, systemic therapy, radiation, and chemoradiation approaches are discussed. For resectable and borderline resectable disease, surgical management and perioperative therapy are reviewed.

Given the multimodality approach of pancreatic cancer, the role of gastroenterologists in the management of the disease is reviewed with emphasis on screening, diagnosis, symptoms management, and endoscopic ultrasound-guided local therapies and fiducial markers placement. Emerging paradigms in pancreatic cancer management are presented, such as minimally invasive surgical approaches, local ablative technologies, emerging radiation approaches, image-based biomarkers, liquid biopsies, and molecular profiling of pancreatic cancer. This book also provides a valuable insight into nutrition and early integration of supportive/palliative care for pancreatic cancer patients.

This textbook will serve as a very useful resource for physicians and scientists dealing with, or interested in, this challenging malignancy. Given the multidisciplinary approach of pancreatic cancer, this book has brought together experts from a variety of integrated disciplines such as gastroenterology, medical oncology, surgical oncology, radiation oncology, pathology, radiology, rehabilitation medicine, and nutrition. The audience for this book

includes medical oncologists, radiation oncologists, surgeons, gastroenterologists, research scientists with interest in pancreatic cancer, fellows and residents training in surgical, radiation, and medical oncology as well as gastroenterology.

All chapters are written by experts in their fields and include the most up-to-date scientific and clinical information. This comprehensive and yet concise state-of-the-art review of this field will help guide patient management and stimulate investigative efforts. This book outlines *The MD Anderson Approach to managing pancreatic cancer,* written mostly by experts from UT MD Anderson Cancer Center with some collaborative colleagues from other institutions. We are extremely grateful to all the contributors for their time and effort in this endeavor.

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Pancreatic Cancer at a Glance

1

Dema Maher Shobaki and Manoop S. Bhutani

Introduction

Cancer incidence and mortality are increasing worldwide, with expectations of becoming the leading cause of death and the biggest inhibitor to increase the life expectancy in every country in the twenty-first century [1]. Since the first description of pancreatic cancer in Giovanni Battista Morgagni's *De Sedibus et Causis Morborum per Anatomen Indigatis* in the 1760s, its global burden continues to rise due to aging, growth in the world's population, and high-risk lifestyles, such as smoking, physical inactivity, and "westernized" diets [2–4]. Known for its very poor prognosis, pancreatic cancer has a low 5-year survival rate of about 5%, regardless of the income status of all countries affected, and the incidence of pancreatic cancer is particularly high within the 60 and 80 years of age [5–7].

The Global Burden of Disease (GBD) study reported the incidence and mortality rates and its risk factors of pancreatic cancer across 195 countries and territories located across 21 regions, for both sexes and 20 age groups, from 1990 to 2017. The GBD reported the number of newly diagnosed pancreatic cancer cases increased from 195,413 in 1990 to 447,664 in 2017, a 129.1% increase observed globally [8]. There was a 125.2% increase in pancreatic cancer deaths worldwide, from 195,861 in 1990 to 441,082 in 2017 [8]. After stratifying 195 countries and territories into five sociodemographic index (SDI) groups, including low, low-middle, middle, high-middle, and high, the most prevalent age-standardized incidence rate (ASIR) occurred in low-middle SDI countries, and the highest increase in pancreatic deaths was detected in the middle SDI quintile [8].

The International Agency for Research on Cancer (IARC), a global institution established by the World Health Organization (WHO), gathered estimates of pancreatic cancer incidence and mortality rates across 185 countries across 21 regions as defined by the United Nations (UN) and published its reporting in the GLOBOCAN 2020 database [9]. Under the GLOBOCAN 2020 project, IARC collected the epidemiological variables of malignant pancreatic neoplasms, with the tenth edition of the International Classification of Diseases (ICD-10 version 2010) category of C25, from various international registries based on each cancer registry's definition of malignancy [9]. Pancreatic incidence and mortality rates by sex and 18 age groups (0–4, 5–9, 10–14,

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_1

15–19 … 75–79, 80–84, 85 and over) were estimated for 185 countries and territories in 2020 [9]. The epidemiological information presented in this chapter is based on data available on Globocan 2020 on March 01, 2021 (December 2020, version 1.0).

Incidence

The incidence rate of new cases of pancreatic cancer was estimated among both sexes and across all ages. In 2020, 495,773 new cases of pancreatic cancer were identified worldwide, with the 13th highest incidence rate among all cancers, representing 2.6% of registered new cases of cancer [10]. Northern America and Europe observed the highest incidence age-standardized rate (ASR), the rate adjusted to account for difference in ages seen in the population, of pancreatic cancer at 8.00 and 7.80 per 100,000 people, respectively, in 2020 when compared to the world at 4.90 per 100,000 people (Table 1.1) [1, 10]. The lowest incidence ASR at 2.30 was seen in Africa followed by Asia with an incidence ASR of 4.00 [1, 10].

Table 1.1 The incidence age-standardized rates (ASR) of pancreatic cancer, the ranking of the pancreatic cancer, and the percentage of new cancer cases in both sexes across six continents when compared to the world in 2020. Data Sourced: GLOBOCAN 2020

Incidence age-standardized rates, world ranking, and percent of new cases of pancreatic cancer, both sexes, across six continents, in 2020				
Populations	Number of New Cases	Incidence, ASR[a]	Cancer Ranking	Percent of New Cases (%)
World	495,773	4.9	13	2.6
Africa	17,070	2.3	18	1.5
Asia	233,701	4.0	13	2.5
Europe	140,116	7.8	8	3.2
Latin America and the Caribbean	37,352	4.5	12	2.5
Northern America	62,643	8.0	11	2.4
Oceania	4891	6.6	11	1.9

[a]Per 100,000 people

Majority of the countries with the highest incidence of pancreatic cancer are located in Europe [10]. The average of the 15 countries with the highest ASR is 9.26, almost twice as much as that seen in the world collectively [10]. Hungary had the highest ASR in the world with 11.20 per 100,000, followed closely by the South American country of Uruguay with an ASR of 10.7 (Table 1.2A). The East African country of Malawi has the lowest incidence in the world, with 0.63 per 100,000, with the Melanesian country of Vanuatu estimated to have an ASR of 0.64 per 100,000 (Table 1.2B) [10]. There is a 178.7% difference in incidence rates between Hungary and Malawi [10].

There is a minor difference in the incidence of pancreatic cancer observed among men and women as well as noticeable difference in geographic distribution [1, 11]. There were more new cases of pancreatic cancer in men (5.70 per 100,000 people) than in women (4.10 per 100,000). The highest incidence rate in males was seen in Hungary, with an incidence rate of 13.70 per 100,000, whereas the lowest incidence rate was seen in Malawi with incidence rate of 0.46 per 100,000 (Table 1.3A, B) [10]. Similar to its male counterparts, the highest incidence rate in females was seen in Hungary with 9.20 per 100,000, a rate of 76.7% more than the world's average rate (Table 1.3C) [10]. Conversely, the lowest rate in females is estimated to be 0.30 per 100,000 in the South-Central Asian country of Pakistan (Table 1.3D) [10].

When stratifying the incidence of disease into 21 United Nations (UN) regions, the risk of developing pancreatic cancer is highest in Western Europe (8.6), then in the Northern America (8.0), followed closely by 7.5 per 100,000 in Central and Eastern Europe [10]. The lowest incidence rates were observed in Southern-Central Asia (1.2), in Middle Africa (1.5), and in Eastern Asia (1.8) (Fig 1.1a–f) [10]. The highest rates of new pancreatic cases in men are in Western Europe (9.9) and Central and Eastern Europe (9.9), followed by Northern America (9.3) [10]. Conversely, the lowest incidence rates in men are in the regions of Southern-Central Asia (1.5), Eastern Africa, and Middle Africa

Table 1.2 (A) The 15 countries with the highest incidence rate (ASR) in 2020, compared to the incidence rate seen in the world. (B) The 15 countries with the lowest incidence rate (ASR) in 2020, compared to the world's incidence rate. Data Sourced: GLOBOCAN 2020

Populations	Cancer—Incidence Ranking	Incidence, ASR[a]
(A) Countries with the highest incidence age-standardized rates of pancreatic cancer in 2020		
World	Not Applicable	4.9
Hungary	1	11.2
Uruguay	2	10.7
Japan	3	9.9
Slovakia	4	9.6
Czechia	5	9.5
Austria	6	9.0
Armenia	7	8.9
Estonia	8	8.9
Malta	9	8.9
Germany	10	8.8
Finland	11	8.8
Latvia	12	8.8
Republic of Moldova	13	8.7
France	14	8.6
Slovenia	15	8.6
(B) Countries with the lowest incidence age-standardized rates of pancreatic cancer in 2020		
World	Not Applicable	4.90
Malawi	1	0.63
Vanuatu	2	0.64
Botswana	3	0.66
Eswatini	4	0.69
Pakistan	5	0.73
Mozambique	6	0.77
Sri Lanka	7	0.81
Rwanda	8	0.88
India	9	0.94
Viet Nam	10	0.97
Guinea	11	0.98
Bangladesh	12	1.00
Angola	13	1.00
Namibia	14	1.00
Djibouti	15	1.00

[a]Per 100,000 people

Table 1.3 (A) The six countries with the highest incidence rates in the male population compared to the world's incidence. (B) The six countries with the lowest incidence rates in the male population. (C) The six countries with the highest incidence rates in the female population when compared to the world's incidence rate of pancreatic cancer. (D) The six countries with the lowest incidence rates in females when compared to the world's incidence rate of pancreatic cancer. Data Sourced: GLOBOCAN 2020

(A) Countries with the highest incidence age-standardized rates of pancreatic cancer, males, all ages, in 2020	
Populations (male)	**Incidence, ASR[a]**
World	5.7
Hungary	13.7
French Guiana	13.0
Uruguay	12.8
Slovakia	12.0
Armenia	11.9
Latvia	11.9
(B) Countries with the lowest incidence age-standardized rates of pancreatic cancer, males, all ages, in 2020	
Populations (male)	**Incidence, ASR[a]**
World	5.70
Malawi	0.46
Eswatini	0.57
Botswana	0.82
Pakistan	1.1
Bangladesh	1.1
Sri Lanka	1.1
Mozambique	1.1
(C) Countries with the highest incidence age-standardized rates of pancreatic cancer, females, all ages, in 2020	
Populations (female)	**Incidence, ASR[a]**
World	4.1
Hungary	9.2
Uruguay	8.9
Japan	8.2
Czechia	8.0
Austria	8.0
Sweden	7.9

(continued)

Table 1.3 (continued)

(D) Countries with the lowest incidence age-standardized rates of pancreatic cancer, females, all ages, in 2020

Populations (female)	Incidence, ASR[a]
World	4.10
Pakistan	0.30
Comoros	0.47
Mozambique	0.53
Rwanda	0.55
Sri Lanka	0.61
Djibouti	0.61

[a]Per 100,000 people

(2.0), followed closely by Western Africa (2.2) [10]. The highest risk in developing pancreatic cancer in women was observed in Western Europe (7.4), in Northern America (6.9), and in Northern Europe and Australia and New Zealand (6.7), while the lowest rates are in Southern-Central Asia (0.88) and in Middle Asia (1.2) [10].

The rate of developing pancreatic cancer increases with age in both the male and female populations (Fig. 1.2, Table 1.4) [1, 11–13]. The age-standardized rates of new cases of pancreatic cancer drastically increase after the age of 54 in both men and women [10]. This may be the result

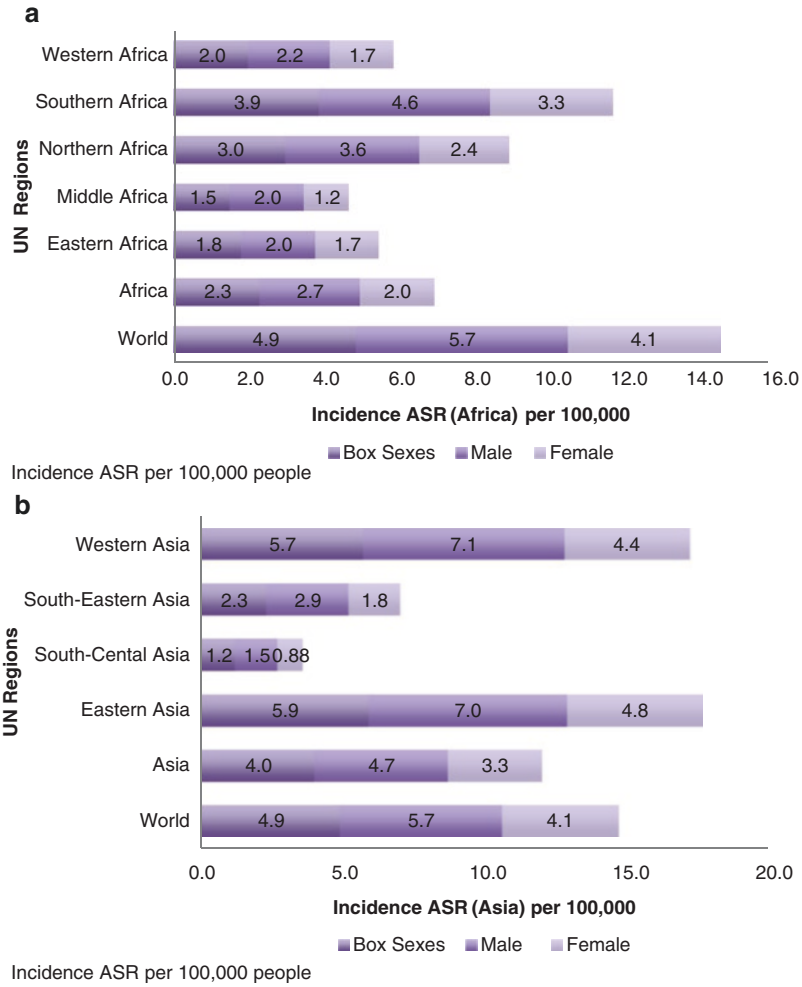
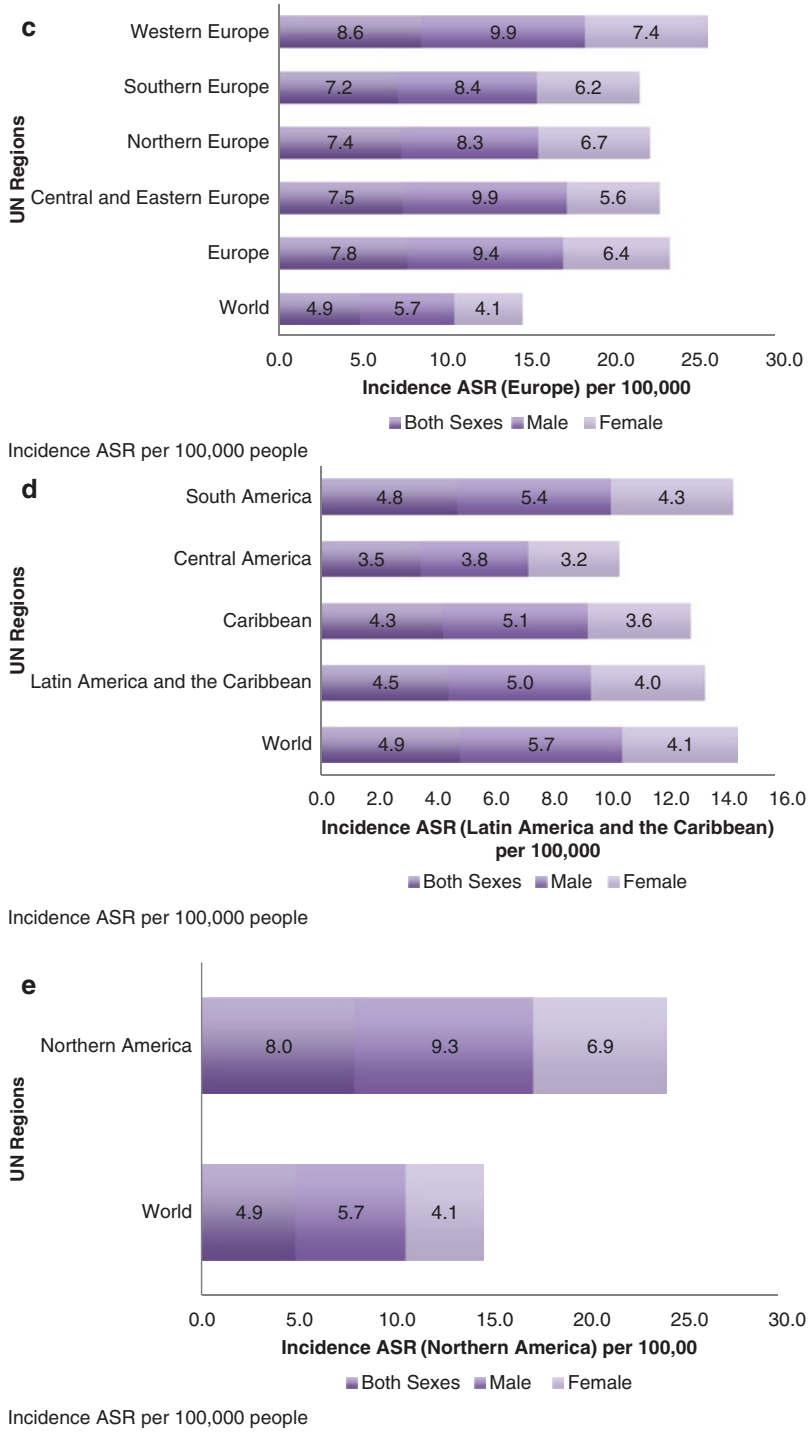


Fig. 1.1 (**a**) The estimated rates of new pancreatic cancer in UN African regions, including both sexes, males, and females, in 2020. (**b**) The estimated rates of new pancreatic cancer in UN Asian regions, including sexes, males, and females, in 2020. (**c**) The estimated rates of new pancreatic cancer in UN European regions, including both sexes, males, and females, in 2020. (**d**) The estimated rates of new pancreatic cancer in UN Latin America and the Caribbean regions, including both sexes, males, and females, in 2020. (**e**) The estimated rates of new pancreatic cancer in UN Northern American regions, including both sexes, males, and females, in 2020. (**f**) The estimated rates of new pancreatic cancer in UN Northern American regions, including both sexes, males, and females, in 2020. Data Sourced: GLOBOCAN 2020



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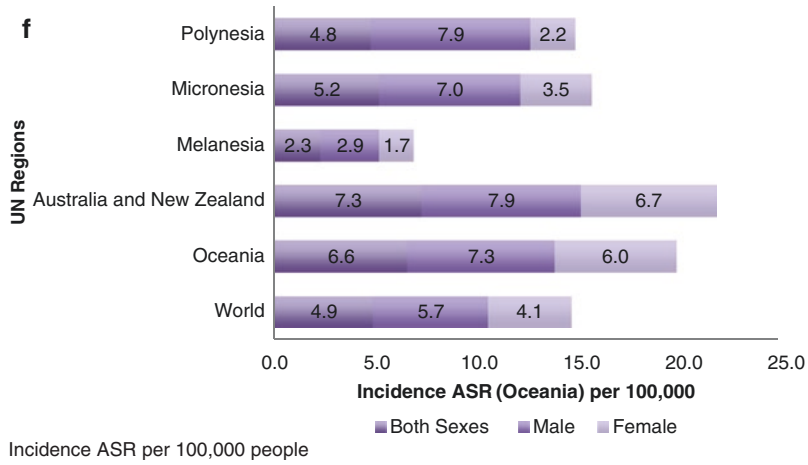

Fig. 1.1 (continued)

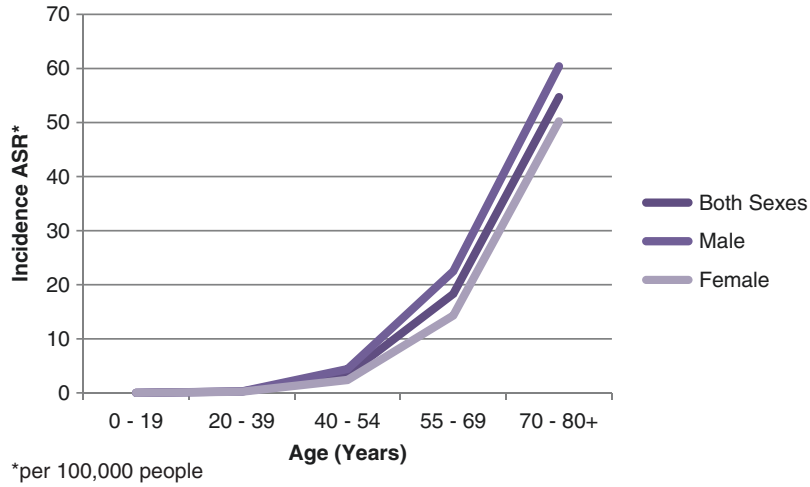

Fig. 1.2 The estimated incidence age-standardized rates of new pancreatic cancer with age, for both sexes, in 2020. Data Sourced: GLOBOCAN 2020

Table 1.4 The estimated incidence age-standardized rates of new pancreatic cancer with age, for both sexes, in 2020. Data Sourced: GLOBOCAN 2020

Estimated incidence age-standardized rates of pancreatic with age, male and female, in 2020			
Populations (age)	Incidence ASR (both sexes)[a]	Incidence ASR (male)[a]	Incidence ASR (female)[a]
0–19	0.01	0.01	0.01
20–39	0.25	0.27	0.22
40–54	3.4	4.4	2.4
55–69	18.3	22.5	14.3
70–85+	54.7	60.4	50.2

[a]Per 100,000 people

of the lack of pancreatic cancer diagnoses prior to the age of 55 [11, 13, 14].

Although the etiology for the incidence rates of pancreatic cancer is not apparent, the exposure to particular risk factors from the environment may explain the difference observed in geographic (see Chap. 2) [11]. The use of various forms of diagnostic modalities and the accuracy, completeness, and coverage of the registries completed in developed and underdeveloped countries may contribute to these differences [11, 15, 16].

Prevalence

Per the International Agency for Research on Cancer, the prevalence of pancreatic cancer is the number of diagnosed individuals who are still alive at a given point in time [10, 17]. The prevalence rate, presented as the proportion of the population with pancreatic cancer per 100,000 people is estimated over 1-year, 3-year, and 5-year time period in 2020. The estimated proportions of the world's cases of pancreatic cancer in 2020 are 2.80 per 100,000 people in a 1-year time period, 4.30 in a 3-year time period, and 4.90 in a 5-year time period [10].

Majority of the countries with the highest prevalence ratios are located in Europe [10]. Within the 1-, 3-, and 5-year time periods, the largest proportion of a population with pancreatic cancer diagnoses is observed in Japan (14.00, 21.00, 23.80), followed by Hungary (10.90, 16.70, 19.20), Germany (10.90, 16.50, 18.70), and Finland (10.80, 16.40, 18.60) (Table 1.5A–C) [10].

Djibouti has the lowest pancreatic cancer prevalence ratio of 0.10 per 100,000 people in their population, followed by Botswana (0.13) and Guinea-Bissau and the Solomon Islands (0.15) within a 1-year time period in 2020 (Table 1.6A) [10]. In reference to a 3-year time period, Malawi and the Solomon Island have the lowest ratio with 0.29 per 100,000 individuals, followed closely by Botswana (0.30) (Table 1.6B) [10]. Botswana has the lowest prevalence ratio of pancreatic cancer in 2020 within a 5-year time period (0.30), with Vanuatu estimating to have 0.33 per 100,000 of their populations living or surviving pancreatic cancer, followed by Malawi (0.36) (Table 1.6C) [10].

Table 1.5 The 15 countries with the highest age-specific ratios of incidence of pancreatic cancer. (A) 1-year estimated prevalence of pancreatic cancer in 2020. (B) 3-year estimated prevalence of pancreatic cancer in 2020. (C) 5-year estimated prevalence of pancreatic cancer in 2020. Data Sourced: GLOBOCAN 2020

(A) Countries with the highest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 1-year estimated prevalence

Populations	1-Year Ranking	1-Year Prevalence[a]	Proportions[b]
World	Not Applicable	214,471	2.80
Japan	1	17,753	14.00
Germany	2	9168	10.90
Hungary	3	1055	10.90
Finland	4	601	10.80
Czechia	5	1079	10.10
Austria	6	878	9.70
Malta	7	43	9.70
Slovenia	8	199	9.60
Switzerland	9	823	9.50
Estonia	10	124	9.30
Sweden	11	930	9.20
France, Guadeloupe	12	37	9.20
France	13	5951	9.10
Italy	14	5523	9.10
Denmark	15	528	9.10

(continued)

Table 1.5 (continued)

(B) Countries with the highest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 3-year estimated prevalence

Populations	3-Year Ranking	3-Year Prevalence[c]	Proportions[b]
World	Not Applicable	331,348	4.30
Japan	1	26,553	21.00
Hungary	2	1616	16.70
Germany	3	13,799	16.50
Finland	4	907	16.40
Czechia	5	1648	15.40
Austria	6	1335	14.80
Malta	7	65	14.70
Slovenia	8	302	14.50
Switzerland	9	1244	14.40
Estonia	10	187	14.10
Sweden	11	1409	14.00
France	12	9036	13.80
Denmark	13	798	13.80
Italy	14	8264	13.70
Latvia	15	258	13.70

(C) Countries with the highest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 5-year estimated prevalence

Populations	5-Year Ranking	5-Year Prevalence[d]	Proportions[b]
World	Not Applicable	379,958	4.90
Japan	1	30,137	23.80
Hungary	2	1851	19.20
Germany	3	15,698	18.70
Finland	4	1032	18.60
Czechia	5	1875	17.50
Austria	6	1521	16.90
Slovenia	7	342	16.50
Malta	8	73	16.50
Switzerland	9	1419	16.40
Estonia	10	212	16.00
Sweden	11	1604	15.90
France	12	10,313	15.80
Denmark	13	910	15.70
Latvia	14	296	15.70
Italy	15	9386	15.50
Greece	16	1611	15.50
Lithuania	17	422	15.50

[a]Computed using sex-, site-, and age-specific ratios of incidence to 1-year prevalence from Nordic countries for the period 2006–2015

[b]Proportions of the population per 100,000 persons

[c]Computed using sex-, site-, and age-specific ratios of incidence to 3-year prevalence from Nordic countries for the period 2006–2015

[d]Computed using sex-, site-, and age-specific ratios of incidence to 5-year prevalence from Nordic countries for the period 2006–2015

Table 1.6 The 15 countries with the lowest sex-, age-specific ratios of incidence of pancreatic cancer. (A) 1-year estimated prevalence of pancreatic cancer in 2020. (B) 3-year estimated prevalence of pancreatic cancer in 2020 (C) 5-year estimated prevalence of pancreatic cancer in 2020. Data Sourced: GLOBOCAN 2020

(A) Countries with the lowest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 1-year estimated prevalence

Populations	**1-Year Ranking**	**1-Year Prevalence[a]**	**Proportions[b]**
World	Not Applicable	214,471	2.80
Djibouti	1	1	0.10
Botswana	2	3	0.13
Guinea-Bissau	3	3	0.15
Solomon Islands	4	1	0.15
Malawi	5	33	0.17
Eswatini	6	2	0.17
Mozambique	7	62	0.20
Angola	8	68	0.21
Guinea	9	28	0.21
Timor-Leste	10	3	0.23
Namibia	11	6	0.24
Rwanda	12	32	0.25
Pakistan	13	579	0.26
Lesotho	14	6	0.28
Sudan	15	125	0.29
Zambia	16	53	0.29
Central African Republic	17	14	0.29

(B) Countries with the lowest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 3-year estimated prevalence

Populations	**3-Year Ranking**	**3-Year Prevalence[c]**	**Proportions[b]**
World	Not Applicable	331,348	4.30
Malawi	1	56	0.29
Solomon Islands	2	2	0.29
Botswana	3	7	0.30
Vanuatu	4	1	0.33
Angola	5	111	0.34
Guinea	6	46	0.35
Mozambique	7	111	0.36
Central African Republic	8	19	0.39
Eswatini	9	5	0.43
Rwanda	10	57	0.44
Eritrea	11	16	0.45
Pakistan	12	1010	0.46
Uganda	13	211	0.46
Sudan	14	206	0.47
Burundi	15	60	0.50

(C) Countries with the lowest sex-, age-specific ratios of incidence of pancreatic cancer in 2020, 5-year estimated prevalence

Populations	**5-Year Ranking**	**5-Year Prevalence[d]**	**Proportions[b]**
World	Not Applicable	379,958	4.90
Botswana	1	7	0.30
Vanuatu	2	1	0.33
Malawi	3	69	0.36
Angola	4	130	0.40

(continued)

Table 1.6 (continued)

Guinea	5	52	0.40
Mozambique	6	134	0.43
Eswatini	7	5	0.43
Solomon Islands	8	3	0.44
Central African Republic	9	23	0.48
Rwanda	10	66	0.51
Guinea-Bissau	11	10	0.51
Uganda	12	243	0.53
Sudan	13	242	0.55
Pakistan	14	1230	0.56
Burundi	15	67	0.56
Eritrea	16	20	0.56

[a]Computed using sex-, site-, and age-specific ratios of incidence to 1-year prevalence from Nordic countries for the period 2006–2015
[b]Proportions of the population per 100,000 persons
[c]Computed using sex-, site-, and age-specific ratios of incidence to 3-year prevalence from Nordic countries for the period 2006–2015
[d]Computed using sex-, site-, and age-specific ratios of incidence to 5-year prevalence from Nordic countries for the period 2006–2015

Mortality

The mortality rates of pancreatic cancer differ around the world. In 2020, the world had 466,003 deaths relating to pancreatic cancer, with a mortality age-standardized rate (ASR) of 4.5 per 100,000 people [10]. Moreover, pancreatic cancer is the world's seventh leading cancer-related death, comprising 4.7% of all cancer-related deaths [10]. Similar to what was observed for the incidence ASR, Europe and North America have the highest mortality ASR at 7.2 and 6.5 per 100,000 people, respectively, with the Oceania region experiencing the third highest mortality rate of 5.2 (Table 1.7) [10]. The lowest mortality rate was estimated to be 2.3 per 100,000 people in Africa, with pancreatic cancer as the 14th leading cause of cancer-related deaths, as of 2020 [10].

Similar to the incidence trends around the world, majority of the countries with the highest mortality age-standardized rates of pancreatic cancer are located in Europe. The Central and Eastern European country of Hungary and the South American country of Uruguay each have the highest mortality ASR in 2020 at 10.2 per 100,000, a difference of 77.6% when compared to the world's average rate, distantly followed by Armenia at 8.6 per 100,000 (Table 1.8A) [10]. The Eastern African country of Malawi has the lowest morality rate in the world, with 0.62 per

Table 1.7 The mortality age-standardized rates (ASR) of pancreatic cancer, the ranking of the pancreatic cancer deaths, and the percentage of cancer deaths in both sexes across six continents when compared to the world in 2020. Data Sourced: GLOBOCAN 2020

Mortality age-standardized rates, world ranking, and percent of new cases of pancreatic cancer, both sexes, across six continents, in 2020				
Populations	Number of Death Cases	Mortality, ASR[a]	Cancer Ranking	Percent of Cancer Deaths (%)
World	466,003	4.5	7	4.7
Africa	16,549	2.3	14	2.3
Asia	224,034	3.8	7	3.9
Europe	132,134	7.2	4	6.8
Latin America and the Caribbean	36,030	4.3	7	5.1
Northern America	53,277	6.5	2	7.6
Oceania	3979	5.2	5	5.7

[a]Per 100,000 people

Table 1.8 (A) The 15 countries with the highest mortality rate (ASR) in 2020, compared to the morality rate seen in the world. (B) The 15 countries with the lowest mortality rate (ASR) in 2020, compared to the world's mortality rate. Data Sourced: GLOBOCAN 2020

Populations	Cancer Mortality Ranking	Mortality, ASR[a]
(A) Countries with the highest mortality age-standardized rates of pancreatic cancer in 2020		
World	Not Applicable	4.5
Hungary	1	10.2
Uruguay	2	10.2
Armenia	3	8.6
Czechia	4	8.5
Finland	5	8.5
Republic of Moldova	6	8.3
Germany	7	8.2
Austria	8	8.1
Serbia	9	8.0
Israel	10	8.0
Slovakia	11	8.0
Montenegro	12	8.0
Estonia	13	7.8
Malta	14	7.8
France, Guadeloupe	15	7.8
(B) Countries with the lowest mortality age-standardized rates of pancreatic cancer in 2020		
World	Not Applicable	4.5
Malawi	1	0.62
Vanuatu	2	0.64
Botswana	3	0.66
Eswatini	4	0.69
Pakistan	5	0.71
Mozambique	6	0.75
Sri Lanka	7	0.80
Rwanda	8	0.85
India	9	0.90
Viet Nam	10	0.92
Bangladesh	11	0.98
Guinea	12	0.98
Angola	13	1.00
Namibia	14	1.00
Djibouti	15	1.00

[a]Per 100,000 people

100,000 people, followed by Vanuatu at 0.64 and Botswana at 0.66 (Table 1.8B) [10]. Asia experienced about 48.1% of the world's pancreatic cancer-related deaths [10, 11].

There was roughly a 33.0% difference in the pancreatic cancer mortality age-standardized rate between males and females in 2020, with the world's rate in males being 5.3 per 100,000 people and 3.8 observed in females [10]. The highest mortality rates in males were seen in the countries of Hungary (12.6) and Uruguay (12.2), whereas the lowest mortality age-standardized rates were seen in Malawi with incidence rate of 0.46 and in the Southern African country of Eswatini with 0.57 per 100,000, respectively (Tables 1.9A, B) [10]. The highest incidence rate in females was seen in Uruguay with 8.5 per 100,000, followed closely by Hungary with a rate of 8.4, and Finland at 7.3 (Table 1.3C) [10]. The lowest mortality rates in females were estimated to be 0.30 per 100,000 in the South-Central Asian country of Pakistan and in the Eastern African country of Comoros (0.47) (Table 1.9C, D) [10].

The world's mortality rates were also stratified into 21 United Nations (UN) regions, and mortality rates were highest in Western Europe with 7.8 per 100,000 people, in Central and Eastern Europe with a rate of 7.1, and in Southern Europe with a rate of 6.6 (Fig. 1.3a–f) [10]. The lowest mortality rates were observed in South-Central Asia (1.1), in Middle Africa (1.5), in and Eastern Africa (1.8) (Fig. 1.3a–f) [10]. The highest rates of pancreatic cancer-related deaths in males were in Central and Eastern Europe (9.6) and in Western Europe (9.1), both with rates higher than Europe's average of 8.8 [10]. The lowest mortality rates in men were in South-Central Asia (1.4) and in Eastern Africa and Middle Africa (2.0) [10]. The highest mortality rates in females were in Western Europe (6.6), in Northern Europe (5.7), and in Northern America and Southern Europe (each at 5.5), while the lowest rates are in South-Central Asia (0.86), in Middle Africa (1.1), and in Melanesia (1.6) [10].

The mortality rates increase with age in both the male and female populations (Fig. 1.4, Table 1.10). Roughly 90.0%, 419,597 out of 466,003 pancreatic cancer-related deaths occur after the age of 55 [1, 10, 11]. The mortality ASR increase was more pronounced in the female pop-

Table 1.9 (A) The six countries with the highest mortality age-standardized rates in the male population compared to the world's mortality rate. (B) The six countries with the lowest mortality age-standardized rates in the male population. (C) The six countries with the highest mortality age-standardized rates in the female population when compared to the world's mortality rate of pancreatic cancer. (D) The six countries with the lowest mortality age-standardized rates in females when compared to the world's mortality rate of pancreatic cancer. Data Sourced: GLOBOCAN 2020

(A) Countries with the highest mortality age-standardized rates of pancreatic cancer, males, all ages, in 2020

Populations (male)	Mortality, ASR[a]
World	5.3
Hungary	12.6
Uruguay	12.2
Armenia	11.5
Republic of Moldova	10.7
Latvia	10.6
Montenegro	10.6

(B) Countries with the lowest mortality age-standardized rates of pancreatic cancer, males, all ages, in 2020

Populations (male)	Mortality, ASR[a]
World	5.30
Malawi	0.46
Eswatini	0.57
Botswana	0.82
India	1.10
Pakistan	1.10
Bangladesh	1.10
Sri Lanka	1.10
Mozambique	1.10

(C) Countries with the highest mortality age-standardized rates of pancreatic cancer, females, all ages, in 2020

Populations (female)	Mortality, ASR[a]
World	3.8
Uruguay	8.5
Hungary	8.4
Finland	7.3
France, Guadeloupe	7.2
Austria	7.1
Czechia	7.0

Table 1.9 (continued)

(D) Countries with the lowest mortality age-standardized rates of pancreatic cancer, females, all ages, in 2020

Populations (female)	Mortality, ASR[a]
World	3.80
Pakistan	0.30
Comoros	0.47
Mozambique	0.52
Rwanda	0.52
Sri Lanka	0.60
Djibouti	0.61

[a]Per 100,000 people

ulation when compared to its male counterpart after the age of 55 [10].

Human Development Index

The incidence and mortality cases of pancreatic cancer were evaluated by low, medium, high, very high Human Development Index (HDI), which is a statistic composite index of life expectancy, education, and gross income. As reported in Table 1.11, pancreatic cancer's incidence and mortality ASRs are positively associated with human development for both sexes [10, 18]. The largest difference in incidence ASR was observed in the high HDI group from the medium HDI at 117.2% [10]. In parallel, there is a 121.4% difference in mortality ASR in the high HDI group [10].

Incidence Projections

The IARC provided their predicted number of new cases of pancreatic cancer in males, females, and both sexes, across the world and its six continents. The projected incidence of pancreatic cancer in the years 2025, 2030, 2035, and 2040 indicates upward trends in all

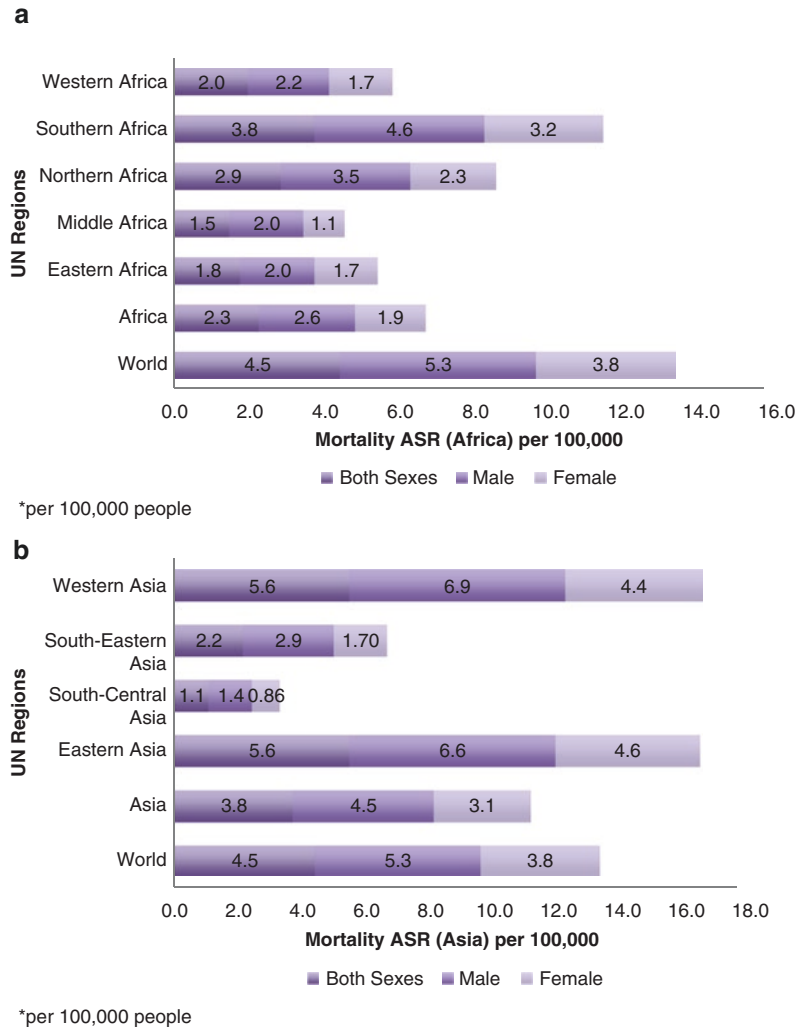

Fig. 1.3 (**a**) The estimated pancreatic cancer-related mortality age-standardized rates in UN African regions, including both sexes, males, and females, in 2020. (**b**) The estimated pancreatic cancer-related mortality age-standardized rates in UN Asian regions, including sexes, males, and females, in 2020. (**c**) The estimated pancreatic cancer-related mortality age-standardized rates in UN European regions, including both sexes, males, and females, in 2020. (**d**) The estimated rates of new pancreatic cancer in UN Latin America and the Caribbean regions, including both sexes, males, and females, in 2020. (**e**) The estimated pancreatic cancer-related mortality age-standardized rates in UN Northern American regions, including both sexes, males, and females, in 2020. (**f**) The estimated pancreatic cancer-related mortality age-standardized rates in UN Northern American regions, including both sexes, males, and females, in 2020. Data Sourced: GLOBOCAN 2020

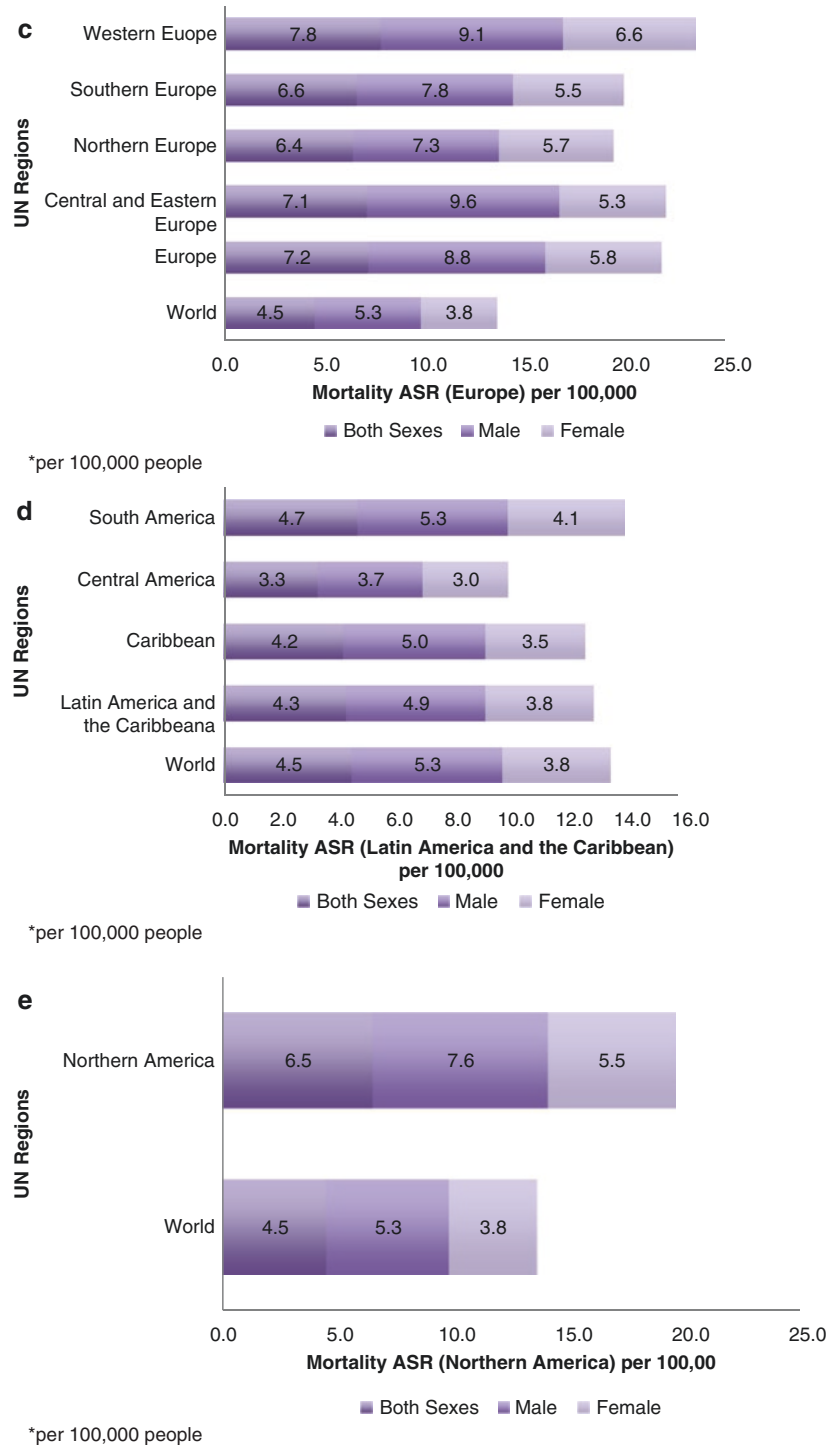

Fig. 1.3 (continued)

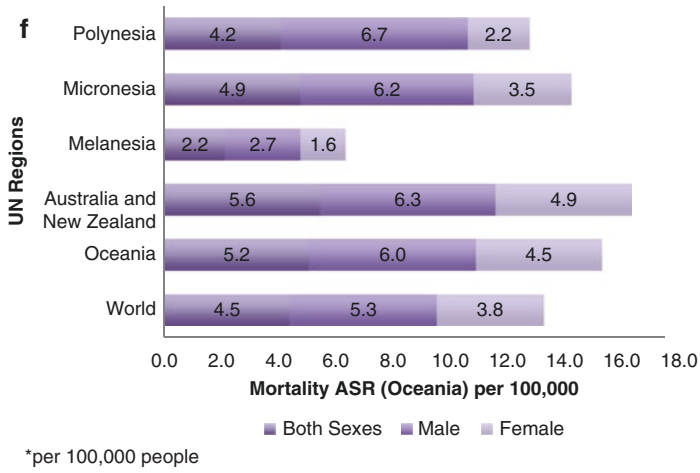

Fig. 1.3 (continued)

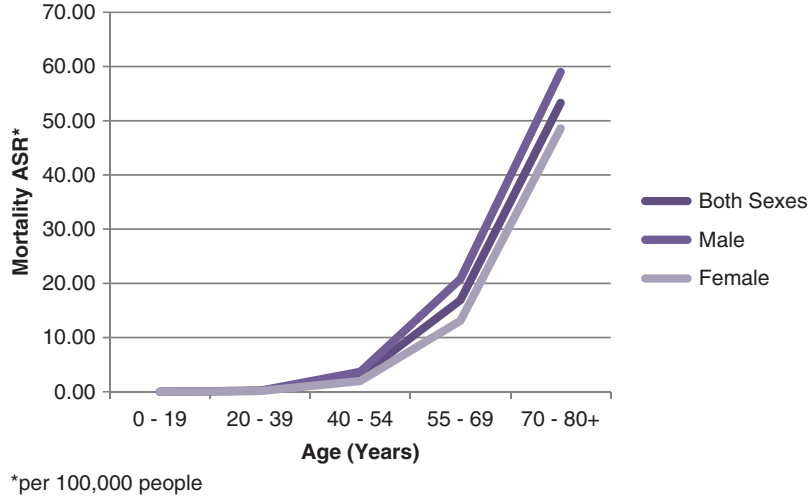

Fig. 1.4 The estimated mortality age-standardized rates of new pancreatic cancer with age, for both sexes, in 2020. Data Sourced: GLOBOCAN 2020

Table 1.10 The estimated mortality age-standardized rates of new pancreatic cancer with age, for both sexes, in 2020. Data Sourced: GLOBOCAN 2020

Estimated mortality age-standardized rates of pancreatic with age, both sexes, in 2020			
Populations (age)	Morality ASR (both sexes)[a]	Mortality ASR (male)[a]	Mortality ASR (female)[a]
0–19	0.00	0.00	0.00
20–39	0.18	0.22	0.14
40–54	2.90	3.70	2.00
55–69	16.90	20.80	13.10
70–85+	53.30	59.00	48.60

[a]Per 100,000 people

six continents when compared to 2020 as baseline (Fig. 1.5). The world is expected to see a 61.7% rise in new cases in 2040, from 2020, with a 60.1% and 63.5% increase in male and female populations, respectively (Table 1.12) [19]. Africa is projected to demonstrate the highest increase in new pancreatic cancer cases with a 100.1% increase from baseline in both sexes, 100.6% and 99.6% increases in male and female populations, respectively, by the year 2040, and the lowest percentage increase, at 27.4%, is predicted to be in Europe, with a

Table 1.11 (A) The relations between the estimated cases of incidence and incidence ASR of pancreatic cancer with the human development indexes seen in both sexes in 2020. (B) The relations between the estimated cases of mortality and mortality ASR of pancreatic cancer with the human development indexes seen in both sexes in 2020. Data Sourced: GLOBOCAN 2020

(A) Estimated number of cases and incidence age-standardized rates of pancreatic cancer with human development index, both sexes, in 2020

HDI	Number	Incidence, ASR[a]	Cancer Ranking	Percentage (%)	Cum. Risk
Low HDI	8586	1.8	19	1.3	0.21
Medium HDI	24,705	1.2	23	1.1	0.14
High HDI	187,205	4.6	11	2.5	0.53
Very high HDI	275,036	7.9	9	3.1	0.92

(B) Estimated number of cases and mortality age-standardized rates of pancreatic cancer with human development index, both sexes, in 2020

HDI	Number	Mortality, ASR[a]	Cancer Ranking	Percentage (%)	Cum. Risk
Low HDI	8355	1.8	14	1.9	0.21
Medium HDI	23,846	1.1	17	1.6	0.14
High HDI	182,247	4.5	7	4.0	0.52
Very high HDI	251,333	6.9	3	7.2	0.80

[a]Per 100,000 people

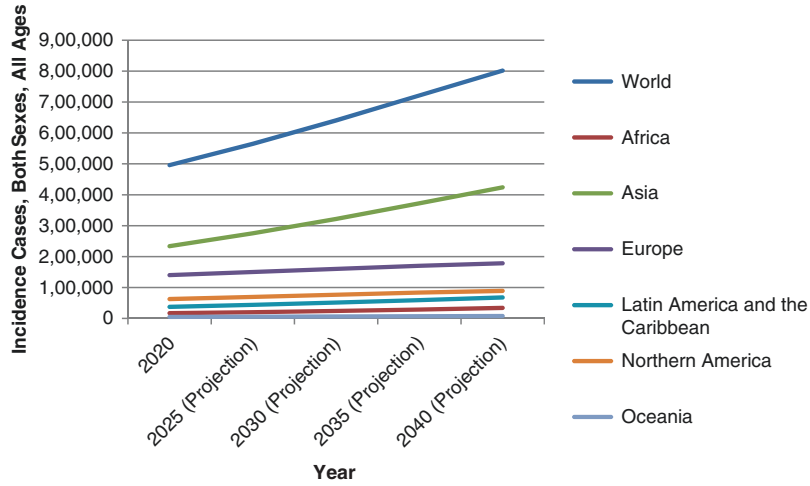

Fig. 1.5 The projected incidence of pancreatic cancer cases, in both sexes, in the years 2025, 2030, 2035, and 2040 across six continents when compared to 2020. Data Sourced: GLOBOCAN 2020

29.2% and 25.5% in both its male and female populations within the same window of time (Table 1.12) [19].

Mortality Projections

The IARC also provides the projected number of pancreatic cancer deaths in males, females, and both sexes, across the world and its six continents. The number of pancreatic cancer-related deaths is expected to increase in the years 2025, 2030, 2035, and 2040 across the six continents when compared to 2020 (Fig. 1.6), with a 64.2% increase globally, a 62.4% increase in the male population, and a 66.2% increase in the female population (Table 1.13) [19]. Similar to the trends predicted for the incidence rates, Africa is projected to experience a 100.7% increase in pancreatic cancer-related deaths by 2040, while Europe is expected to have the smallest increase of 28.5% (Table 1.13) [19].

Table 1.12 The projected incidence of pancreatic cancer cases and demographic changes, in males, females, both sexes, in the years 2025, 2030, 2035, and 2040 across six continents when compared to 2020. Data Sourced: GLOBOCAN 2020

Projected incidence of pancreatic cancer and demographic changes, both sexes, across six continents and 20 years, in 2020													
Population	2020	2025	Number Change	Percentage Change (%)	2030	Number Change	Percentage Change (%)	2035	Number Change	Percentage Change (%)	2040	Number Change	Percentage Change (%)
World (both sexes)	495,773	564,930	69,157	+13.9	640,456	144,683	+29.2	721,261	225,488	+45.5	801,634	305,861	+61.7
World (male)	262,865	299,791	36,926	+14.0	339,280	76,415	+29.1	380,483	117,618	+44.7	420,824	157,959	+60.1
World (female)	232,908	265,137	32,229	+13.8	301,174	68,266	+29.3	340,778	107,870	+46.3	380,808	147,900	+63.5
Africa (both sexes)	17,070	20,228	3158	+18.5	24,079	7009	+41.1	28,706	11,636	+68.2	34,165	17,095	+100.1
Africa (male)	9239	10,962	1723	+18.6	13,061	3822	+41.4	15,576	6337	+68.6	18,538	9299	+100.6
Africa (female)	7831	9266	1435	+18.3	11,017	3186	+40.7	13,130	5299	+67.7	15,627	7796	+99.6
Asia (both sexes)	233,701	275,390	41,689	+17.8	321,786	88,085	+37.7	372,412	138,711	+59.4	424,138	190,437	+81.5
Asia (male)	129,488	151,770	22,282	+17.2	176,042	46,554	+36.0	201,795	72,307	+55.8	227,435	97,947	+75.6
Asia (female)	104,213	123,619	19,406	+18.6	145,744	41,531	+39.9	170,617	66,404	+63.7	196,703	92,490	+88.8
Europe (both sexes)	140,116	150,137	10,021	+7.2	160,250	20,134	+14.4	170,138	30,022	+21.4	178,438	38,322	+27.4
Europe (male)	70,210	75,782	5572	+7.9	81,279	11,069	+15.8	86,406	16,196	+23.1	90,717	20,507	+29.2
Europe (female)	69,906	74,354	4448	+6.4	78,970	9064	+13.0	83,732	13,826	+19.8	87,720	17,814	+25.5
Latin America and Caribbean (both sexes)	37,352	43,866	6514	+17.4	51,207	13,855	+37.1	59,297	21,945	+58.8	67,836	30,484	+81.6
Latin America and Caribbean (male)	18,477	21,633	3156	+17.1	25,150	6673	+36.1	28,981	10,504	+56.8	33,010	14,533	+78.7
Latin America and Caribbean (female)	18,875	22,233	3358	+17.8	26,057	7182	+38.1	30,316	11,441	+60.6	34,826	15,951	+84.5
Northern America (both sexes)	62,643	69,699	7056	+11.3	76,741	14,098	+22.5	83,519	20,876	+33.3	89,124	26,481	+42.3

(continued)

Table 1.12 (continued)

Projected incidence of pancreatic cancer and demographic changes, both sexes, across six continents and 20 years, in 2020													
Population	2020	2025	Number Change	Percentage Change (%)	2030	Number Change	Percentage Change (%)	2035	Number Change	Percentage Change (%)	2040	Number Change	Percentage Change (%)
Northern America (male)	32,938	36,758	3820	+11.6	40,471	7533	+22.9	44,060	11,122	+33.8	47,099	14,161	+43.0
Northern America (female)	29,705	32,941	3236	+10.9	36,270	6565	+22.1	39,459	9754	+32.8	42,025	12,320	+41.5
Oceania (both sexes)	4891	5610	719	+14.7	6393	1502	+30.7	7189	2298	+47.0	7933	3042	+62.2
Oceania (male)	2513	2886	373	+14.8	3277	764	+30.4	3665	1152	+45.8	4025	1512	+60.2
Oceania (female)	2378	2724	346	+14.6	3116	738	+31.0	3524	1146	+48.2	3907	1529	+64.3

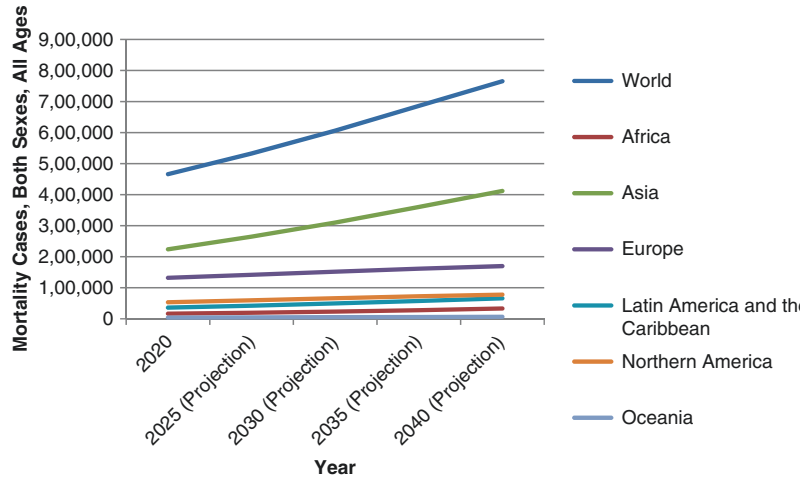

Fig. 1.6 The projected number of pancreatic cancer mortality cases, in both sexes, in the years 2025, 2030, 2035, and 2040 across six continents when compared to 2020. Data Sourced: GLOBOCAN 2020

Conclusion

With the IARC's reporting of the high incidence and mortality age-standardized rates of pancreatic cancer and its unsettling projections by the year 2040, it is imperative to recognize country and continent-specific trends in order to strategically reduce its burden globally, through early screening practices in high-risk individuals, developing new therapeutic strategies and the identification of risk factors that prominently contribute to its poor prognosis and low 5-year survival rate.

Table 1.13 The projected mortality of pancreatic cancer cases and demographic changes, in males, females, both sexes, in the years 2025, 2030, 2035, and 2040 across six continents when compared to 2020. Data Sourced: GLOBOCAN 2020

Projected mortality of pancreatic cancer and demographic changes, both sexes, across six continents and 20 years, in 2020													
Population	2020	2025	Number Change	Percentage Change (%)	2030	Number Change	Percentage Change (%)	2035	Number Change	Percentage Change (%)	2040	Number Change	Percentage Change (%)
World (both sexes)	466,003	532,772	66,769	+14.3	606,316	140,313	+30.1	685,695	219,692	+47.1	765,261	299,258	+64.2
World (male)	246,840	282,460	35,620	+14.4	320,821	73,981	+30.0	361,171	114,331	+46.3	400,988	154,148	+62.4
World (female)	219,163	250,312	31,149	+14.2	285,493	66,330	+30.3	324,526	105,363	+48.1	364,274	145,111	+66.2
Africa (both sexes)	16,549	19,618	3069	+18.5	23,365	6816	+41.2	27,876	11,327	+68.4	33,209	16,660	+100.7
Africa (male)	8936	10,607	1671	+18.7	12,644	3708	+41.5	15,092	6156	+68.9	17,980	9044	+101.2
Africa (female)	7613	9011	1398	+18.4	10,720	3107	+40.8	12,784	5171	+67.9	15,229	7616	+100.0
Asia (both sexes)	224,034	264,630	40,596	+18.1	310,100	86,066	+38.4	360,182	136,148	+60.8	411,834	187,800	+83.8%
Asia (male)	123,337	144,969	21,632	+17.5	168,682	45,345	+36.8	194,057	70,720	+57.3	219,571	96,234	+78.0
Asia (female)	100,697	119,661	18,964	+18.8	141,418	40,721	+40.4	166,125	65,428	+65.0	192,263	91,566	+90.9%
Europe(both sexes)	132,134	141,855	9721	+7.4	151,769	19,635	+14.9	161,539	29,405	+22.3	169,814	37,680	+28.5
Europe (male)	66,698	72,131	5433	+8.1	77,546	10,848	+16.3	82,672	15,974	+23.9	87,037	20,339	+30.5
Europe (female)	65,436	69,724	4288	+6.6	74,223	8787	+13.4	78,868	13,432	+20.5	82,777	17,341	+26.5
Latin America and Caribbean (both sexes)	36,030	42,389	6359	+17.6	49,575	13,545	+37.6	57,518	21,488	+59.6	65,917	29,887	+83.0
Latin America and Caribbean (male)	17,897	20,991	3094	+17.3	24,447	6550	+36.6	28,224	10,327	+57.7	32,203	14,306	+79.9
Latin America and Caribbean (female)	18,133	21,398	3265	+18.0	25,128	6995	+38.6	29,295	11,162	+61.6	33,714	15,581	+85.9
Northern America (both sexes)	53,277	59,693	6416	+12.0	66,249	12,972	+24.3	72,635	19,358	+36.3	77,902	24,625	+46.2
Northern America (male)	27,888	31,359	3471	+12.4	34,762	6874	+24.6	38,050	10,162	+36.4	40,810	12,922	+46.3

Northern America (female)	25,389	28,334	2945	+11.6	31,486	6097	+24.0	34,585	9196	+36.2	37,093	11,704	+46.1
Oceania (both sexes)	3979	4587	608	+15.3	5258	1279	+32.1	5945	1966	+49.4	6585	2606	+65.5
Oceania (male)	2084	2403	319	+15.3	2740	656	+31.5	3076	992	+47.6	3387	1303	+62.5
Oceania (female)	1895	2184	289	+15.3	2518	623	+32.9	2869	974	+51.4	3198	1303	+68.8

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2 Risk Factors and Genetic Predisposition

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Pancreatic cancer (PC)—a rapidly lethal malignancy with an overall 5-year survival rate of 9%—is the third leading cause of cancer-related mortality in the USA [1] and the seventh worldwide [2]. In the USA each year, an estimated 56,770 people will be diagnosed and 45,750 will die of PC [1]. Incidence is on the rise: the disease has been projected to become the second most common cause of cancer death in the USA by 2030 [3]. The most common type of PC (over 90% of cases) is pancreatic ductal adenocarcinoma formed in pancreatic exocrine cells where food-digesting enzymes are made. No effective early detection strategy exists for PC, which contributes to the late diagnosis of most cases. Because the disease is relatively rare, has rapid fatality rates, and presents difficulties in accurate diagnosis, the epidemiological study of PC has been challenging. Known risk factors for PC include age, cigarette smoking, obesity, long-term diabetes, heavy alcohol consumption, chronic pancreatitis, and family history [4]. Most PC patients are diagnosed between ages 60 and 80 and are rarely below age 45. Men and women are affected equally. In the USA, African Americans have 30–40% higher incidence and mortality rates compared to non-Hispanic Whites [5]; epidemiological investigation of racial differences in known risk factors for the disease is inconsistent [6, 7].

Smoking

Cigarette smoking—the most consistently established lifestyle risk factor for PC—accounts for about 25% of disease cases [8]. In general, cigarette smoking increases the risk of PC by 1.5- to two fold. In a meta-analysis of combined results from 42 case-control-, 35 cohort-, and 5 nested case-control studies, the pooled relative risk (RR) estimate for PC was 1.74 (95% CI: 1.61–1.87) for current and 1.2 (95% CI: 1.11–1.29) for former smokers [9]—very similar to data reported by the Pancreatic Cancer Cohort Consortium (PanScan) (RR = 1.77; 95% CI: 1.38–2.26 for current smokers) [10] and the Pancreatic Cancer Case Control Consortium (PanC4) (RR = 1.2; 95% CI: 1.0–1.3 for former smokers) [11]. A dose–response relationship was observed between PC risk and the intensity (number of cigarettes smoked per day), duration (years having smoked), and cumulative smoking dose (number of pack-years) [10, 11]. Although smoking cessation reduces the risk for PC, the risk does not match that of never-smokers until more than 5 to 10 years after quitting [10–12]. Chewing tobacco or smoking cigars or pipes have also been implicated in the risk for PC, but with less

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_2

consistent evidence [9, 13–15], perhaps due to the low prevalence of non-cigarette tobacco products.

Cigarette smoke contains a large amount of chemical carcinogens including nitrosamines, polycyclic aromatic hydrocarbons, and alkylating agents. Although nicotine itself is not carcinogenic, its metabolites, i.e. tobacco-specific nitrosamines, are established human carcinogens and potent pancreatic carcinogens in experimental animals. Tobacco carcinogens may contribute to PC development via DNA damage and gene mutations or by activating pro-tumorigenic signaling pathways [16–18]. Because only a small number of smokers are affected by PC, both genetic- and unidentified non-genetic factors may play a crucial role in determining risk for smoking-related PC. More evidence that supports genetic susceptibility to smoking-related PC is emerging [19, 20].

Obesity

Obesity—another major modifiable risk factor for PC—has been attributed to the development of more than 25% of PC [21]. Obesity is also a risk factor for diabetes, a condition that has a complex relationship with pancreatic cancer (see the next chapter). Obesity is defined by body mass index (BMI), the ratio of weight in kilograms (kg) to height in meters squared (m^2). Overweight and obese are defined by a BMI of 25 to <30 and ≥30 kg/m^2, respectively. Because weight loss is a common symptom of PC, retrospective studies on BMI and PC that rely on self-reported or measured weight a year before or at the cancer diagnosis may be subject to a reverse causation problem. Nevertheless, the association of obesity and increased risk of PC has been consistently reported in several large-scale pooled- and meta-analyses of prospective studies [22–25]. In one meta-analysis of 21 independent prospective studies, involving 3,495,981 individuals and 8062 PC cases, the estimated summary RR of PC per each 5 kg/m^2 increase in BMI was 1.12 (95% CI: 1.06–1.17) in men and women combined, 1.16 (1.05–1.28) in men, and 1.10 (1.02–1.19) in women [22]. Similar findings were reported for men and women in another meta-analysis (RR for a 5 unit BMI increment was 1.10 (95% CI: 1.07–1.14)) [25]. In a nested case-control study including 2170 cases and 2209 controls from PanScan [23], the adjusted OR for the highest vs lowest BMI quartile was 1.33 (95% CI: 1.12–1.58). Interestingly, in a pooled analysis of 14 cohort studies of 846,340 individuals, overweight in early adulthood was associated with a 30% increased risk for PC (95% CI: 1.09–1.56) [24]—consistent with findings from several studies that linked overweight or obesity during adolescence and early adulthood to a greater risk of PC [26–28]. An American Association of Retired Persons cohort study found that duration of overweight increased risk for PC by 6% for every 10 years of being overweight [29]. These findings suggest that maintaining a normal BMI, especially while younger, may reduce PC risk.

Because BMI reflects heaviness and not a distribution of body fat, a number of studies have collected data using indicators of central adiposity, such as waist circumference or waist-to-hip ratio. Using these measures, central adiposity has been associated with increased risk of PC [24, 25, 29–32]. Based on findings from 23 cohort- and 15 case-control studies, a World Cancer Research Fund panel concluded that a convincing and a probable increased risk of PC was related to body and abdominal fatness, respectively [2].

Obesity is recognized as a systemic, low-grade inflammatory condition wherein fat tissue acts as an endocrine organ that regulates synthesis and release of hormones, cytokines, and reactive oxygen species [33]. These adipokines contribute to a state of chronic inflammation and insulin resistance, two major biological mechanisms that underlie obesity-related PC [34–37]. A large amount of experimental evidence points to a tumor-promoting role of insulin and insulin-like growth factors. A number of prospective studies tested blood samples collected 2 to 5 years before diagnosis and found an association between risk of PC and elevated glucose and insulin levels [38]. Inflammation triggered by obesity inhibits or deregulates autophagy, creating an environment that facilitates the induction

and progression of PC [39]. Research with animal models suggests that obesity is not only associated with pancreatic inflammation, but also with increased fatty infiltration and expression of adipokines [36]. This fatty pancreatic disease (not caused by excessive alcohol intake) has been linked to insulin resistance, obesity, and metabolic syndrome and subsequent development of pancreatic and metabolic complications [40].

Alcohol

How alcohol consumption affects PC is more difficult to define because heavy alcohol use—the most common cause of chronic pancreatitis—is also a known risk factor for PC. Furthermore, heavy alcohol drinkers often tend to be smokers so the association of alcohol use and PC could be confounded by smoking. While findings on the associations of alcohol use and PC are inconsistent in many small scale studies [41], two recent large-scale pooled analyses of data from 14 cohort- [42] and 10 case-control studies [43] found an association between heavy alcohol consumption and 22% to 66% increased risk of PC. A large prospective study with more than 6500 never-smokers showed that, compared to non-drinkers, heavy drinkers (more than 3 drinks per day) had a significantly increased risk of PC [44]. In the PanC4 study [43] and in another meta-analysis of 21 case-control and 11 cohort studies [45], the association between heavy alcohol use and increased risk of PC did not substantially change after controlling for history of pancreatitis or smoking status. This supports the notion that heavy alcohol consumption could act as an independent risk factor for PC. However, because of the low prevalence of heavy alcohol drinking reported in most populations, alcohol accounts for only a small portion of all PC. According to a summary review on data from 117 meta- or pooled analyses [8], the population-attributable fractions of the five major risk factors (previously described) for PC are presented in Table 2.1. These data suggest that a large proportion of PC is preventable by maintaining a healthy lifestyle, i.e. avoiding smoking, consuming no or moderate alcohol, and maintaining a normal body weight.

Table 2.1 Population-attributable fraction of major risk factors for pancreatic cancer

Risk factor	Population exposed (%)	Relative risk (%)	Attributable fractions (%)
Tobacco smoking	25–40	1.5–2.2	11–32
Obesity	20–40	1.2–1.5	3–16
Heavy alcohol use	5–20	1.1–1.5	2–9
Chronic pancreatitis	0–1	2.7–5.1	<3
Family history	5–10	1.7–1.8	3–7

Chronic Pancreatitis

Accumulating evidence points to longstanding pre-existing chronic pancreatitis as a strong risk factor for PC [46]. A meta-analysis of 12 case-control and 10 cohort studies [47] reported a statistically significant increase in PC risk for all types of pancreatitis, with summary RRs of 5.1 (95% CI: 3.5–7.3) for unspecified pancreatitis, 13.3 (6.1–28.9) for chronic pancreatitis, and 69.0 (56.4–84.4) for hereditary pancreatitis. In a pooled [48] and a meta-analysis [49], the association between pancreatitis and PC was much stronger among patients with 2 or more years between the diagnosis of pancreatitis and PC, probably reflecting both reverse causation and antecedent misdiagnosis of PC as pancreatitis. Even though the link between chronic pancreatitis and PC is strong, only about 5% of patients with chronic pancreatitis will develop PC [47], while only 1.34% (95% CI: 0.612–2.07%) of PC is attributable to pancreatitis. Thus, PC screening of patients with chronic pancreatitis is not recommended at this time.

Family History

A family history of PC is reported among 10–12% of PC cases and has been associated with an 80% increased risk of PC in a meta-analysis of 9- [50]

and a pooled analysis of 10 cohort studies [51]. Individuals with at least one affected first-degree relative have a 76% (95% CI: 1.19–2.61) increased risk of PC. That risk is even higher in individuals with familial PC (i.e. two or more first-degree relatives affected (OR = 4.26, 95% CI: 0.48–37.9)) [51]. In familial PC, risk also increases with the number of first-degree relatives affected [52]. Based on family-history data, researchers have established a successful in-clinic risk-prediction model for PC-risk counseling and early screening in asymptomatic individuals [53].

Genetic Predisposition

Not all individuals with known risk factors develop PC. The fact that family history is a risk factor for PC suggests that genetic factors play an important role in this disease. Roughly 8% to 30% of patients with familial pancreatic cancer harbor inherited genetic mutations in known cancer-risk genes (including *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, and *STK11*) and in genes associated with other inherited diseases (e.g. *PRSS1* and *CFTR*) (Table 2.2). These rare genetic variations, medium- or high penetrance genes, are often associated with a high or very high lifetime risk of developing PC. Functionally, these genes are involved in cell injury (*PRSS1*, *CTFR*); cell growth and cell cycle control (*ATM*, *CDKN2A*, and *STK11*); and DNA-repair pathways (*BRCA1/2*, *PALB2*, *MSH2*, *MLH1*, *PMS2*, and *FANC* genes) [68]. A large case-control study investigated whether these inherited germline mutations are associated with increased risk of sporadic (non-inherited) PC [69]. Results showed that mutations of the *CDKN2A*, *TP53*, *MLH1*, *BRCA1*, *BRCA2*, and *ATM* genes were present in 5.2% of patients *without* a family history of PC and were positively associated with increased risk of PC. With the rapid development of genome sequencing technology, more susceptibility genes will be discovered for PC.

The recently developed polygenic theory for complex disease inheritance suggests that many disease-predisposing genetic loci exist but only with a small to moderate effect size [70, 71]. To identify how low-penetrance common-susceptibility loci contribute to the development of PC, six large genome-wide association studies (GWAS) were conducted in populations of European ancestry by PanScan and PanC4 consortia [72–77]. To date, 18 susceptibility loci carrying 22 independent single-nucleotide polymorphisms have been identified that surpass the genome-wide significance threshold ($P < 5 \times 10^{-8}$) (Table 2.3).

Table 2.2 Susceptibility genes for pancreatic cancer

Gene	Syndrome	Chromosome location	Estimated relative risk	Reference
PRSS1	Hereditary pancreatitis	7q35	53–67	[54, 55]
CFTR	Cystic fibrosis	7q31.2	5	[56]
STK11/ LKB1	Peutz–Jeghers syndrome	19p13.3	132	[57]
BRCA1 *BRCA2*	Hereditary breast ovarian cancer	17q21 13q12.3	2.3–3.6 3–10	[58, 59]
CDKN2A/ P16	Familial atypical multiple Mole melanoma	9p21	13–22	[60, 61]
APC	Familial adenomatous polyposis	5q21	5	[62]
MSH2 *MLH1* *PMS2*	Hereditary nonpolyposis colorectal cancer	2p21 3p22.2 7p22.1	9	[63]
PALB2	Breast and pancreatic cancer	16p12.2	Unknown	[64]
ATM	Ataxia-telangiectasia	11q22-q23	Unknown	[65]
FANCC *FANCG* *FANCM*	Fanconi anemia	9q22.32 9p13.3 14q21.1	Unknown	[66, 67]

Table 2.3 GWAS top hits for pancreatic cancer

Study (reference)	Single-nucleotide polymorphism	Chromosome	Gene	*P* value	OR (95% CI)
PanScan I [72]	rs505922	9q34.2	*ABO*	5.4×10^{-8}	1.20 (1.12–1.28)
PanScan II [73]	rs9543325	13q22.1	*KLF5?*	3.3×10^{-11}	1.26 (1.18–1.35)
	rs3790844	1q32.1	*NR5A2*	2.5×10^{-10}	0.77 (0.71–0.84)
	rs401681	5p15.33	*CLPTM1L-TERT*	3.7×10^{-7}	1.19 (1.11–1.27)
PanScan III [74]	rs6971499	7q32.3	*LINC-PINT*	3.0×10^{-12}	0.79 (0.74–0.84)
	rs7190458	16q23.1	*BCAR1*	1.1×10^{-10}	1.46 (1.30–1.65)
	rs9581943	13q12.2	*PDX1*	2.4×10^{-9}	1.15 (1.10–1.20)
	rs16986825	22q12.1	*ZNRF3*	1.2×10^{-8}	1.18 (1.12–1.25)
	rs2736098	5p15.33	*TERT*	9.8×10^{-14}	0.80 (0.76–0.85)
PanC4 [75]	rs11655237	17q25.1	*LINC00673*	1.4×10^{-14}	1.26 (1.19–1.34)
	rs17688601	7p14.1	*SUGCT*	1.4×10^{-8}	0.88 (0.84–0.92)
	rs9854771	3q28	*TP63*	2.4×10^{-8}	0.89 (0.85–0.93)
	s1486134	2p14	*ETAA1*	3.4×10^{-9}	1.14 (1.09–1.19)
	rs1561927	8q24.1	*MYC-PVT1*	1.3×10^{-7}	0.87 (0.83–0.92)
Meta-analysis [77]	rs13303010	1p36.33	*NOC2L*	8.4×10^{-14}	1.26 (1.19–1.35)
	rs2941471	8q21.11	*HNF4G*	6.6×10^{-10}	0.89 (0.85–0.93)
	rs4795218	17q12	*HNF1B*	1.3×10^{-8}	0.88 (0.84–0.92)
	rs1517037	18q21.32	*GRP*	3.3×10^{-8}	0.86 (0.80–0.91)
	rs73328514	7p12	*TNS3*	4.4×10^{-8}	0.83 (0.77–0.88)
Imputation [76]	rs2816938	1q32.1	*NR5A2*	4.9×10^{-15}	1.20 (1.15–1.25)
	rs10094872	8q24.21	*MYC*	3.2×10^{-9}	1.15 (1.10–1.20)
	rs35226131	5p15.33	*TERT*	1.7×10^{-8}	0.71 (0.63–0.80)

Topping the list for PC GWAS hits is an *ABO* gene variant important for forming A-, B-, and O blood group proteins (Table 2.3). Individuals with genetically inferred or serologically measured A, AB, and B blood groups may have an increased risk of PC as compared with the O group. Estimates predict that up to 19.5% of PC could be attributed to the non-O blood types [78, 79]. However, the mechanisms that underlie the association of ABO blood groups and PC risk are not understood.

Other GWAS top hits for PC include a group of genes (e.g. *NR5A2*, *PDX1*, and *HNF1B*) coding for transcription factors that regulate the development, differentiation, and functions of the pancreas; a region on chr5p15.33 containing the *TERT* and *CLPTM1* genes; two loci on chr13q22.1 and 7q32.3 that are flanked by genes encoding transcription factors of the Kruppel-like family KLF5, KLF12, and KLF14; the *BCAR1* gene on 16q23.1; and the *ZNF3* gene on 22q12.1 [38]. As most variants discovered in GWAS are usually not functional- or protein-coding variants, much work is needed to fine map and functionally characterize these variants and uncover the biological mechanism related to risk association. Furthermore, research is ongoing on genome sequencing of rare variants that modify the risk of PC, on searching for susceptibility genes among minority ethnic groups, and on demonstrating gene interactions with known risk factors. These efforts will increase our knowledge of genetic susceptibility to PC and offer the opportunity for improved risk assessment.

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3 Pancreatic Cancer and Diabetes Mellitus

Suresh Chari and Anam Khan

Background

In the United States (US), pancreatic cancer is the tenth most common cancer diagnosis; however, it is the third most common cause of cancer death [1]. Recent estimates suggest that in less than a decade, pancreatic cancer will be the second most common cause of cancer death in the US. The 5-year survival rate in all patients with pancreatic cancer is only ~9% and has only marginally improved over the past five decades [2]. Therefore, extensive efforts are underway for early detection of PDAC. The United States Prevention and Screening Task Force recommends against screening for pancreatic cancer in asymptomatic adults. The focus of early detection efforts is on identifying a high-risk group (HRG) that will benefit from regular surveillance. A HRG for sporadic PDAC has been identified in patients at least 50 years of age with new-onset diabetes (NOD).

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Multidirectional Interaction Between DM and PDAC (Fig. 3.1)

Though the relationship between diabetes mellitus (DM) and pancreatic cancer has been known for over 125 years [3], it is incompletely understood. Multiple clinical, epidemiological, laboratory, and experimental studies have examined the complex relationship between the two diseases.

The prevalence of type 2 DM in patients with PDAC ranges from 4% to 65%, depending on how diabetes is diagnosed [4–6]. Epidemiologic studies suggest that long-standing type 2 DM is a modest risk factor for the development of sporadic PDAC. Meta-analysis of multiple cohort and case-control studies shows that the risk of PDAC in patients with type 2 DM for greater than 5 years is 1.5 to 2.0-fold higher than the general population [7, 8]. This is not fully explained by shared risk factors between the two diseases such as obesity and insulin resistance. However, this risk is not sufficient to cost-effectively screen all patients with type 2 DM for PDAC. PDAC also causes established type 2 DM and impaired glucose tolerance to worsen and for DM to become difficult to control. Some studies have suggested that sudden worsening of long-standing DM may be a clue to underlying PDAC [9–11]. Importantly, among patients with PDAC and DM, majority (~75%) of diabetes is new-onset diabetes (NOD), i.e., less than 3 years in duration [12, 13] suggesting that NOD may be caused by pancreatic cancer.

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_3

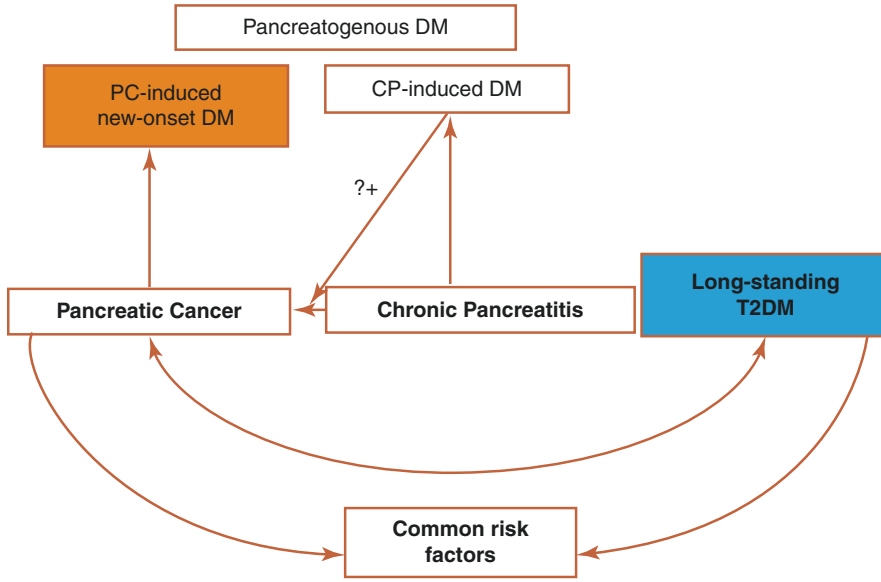

Fig. 3.1 Complex inter-relationship between pancreatic cancer and diabetes

Pathogenesis of Glycemic Disturbance due to PDAC

There are many hypotheses for pathogenesis of diabetes associated with pancreatic cancer [14].

1. Is PC-DM an unmasking of preexisting type 2 diabetes mellitus? Despite the presence of shared risk factors between type 2 DM (e.g., older age, obesity, and family history of DM) and PC-DM, they appear to be distinct clinical entities. The prevalence of NOD and hyperglycemia in 85% of patients with PDAC suggests a cancer related stressor that consistently and profoundly decompensates glucose homeostasis. Also, unlike patients with type 2 DM, glucose control worsens in patients with PDAC in the setting of ongoing, often profound, weight loss.
2. Is PC-DM a consequence of profound cachexia associated with PDAC? Although cancer related cachexia is associated with insulin resistance and disruption of glucose homeostasis, especially in the elderly, it is unlikely to lead to insulin resistance in PDAC [15]. This is because cachexia in PDAC patients is a late finding and has been observed 6 months prior to PDAC diagnosis compared to NOD which occurs 2–3 years prior to the PDAC diagnosis.
3. Is PC-DM due to pancreatic duct obstruction and consequent pancreatic atrophy? PDAC is frequently associated with obstructive pancreatitis and distal atrophy. However, onset of PC-DM occurs before visible appearance of a mass on imaging studies rendering this hypothesis unlikely. Further, insulin levels would be low in patients with DM due to destruction of islet cell mass, while insulin levels are relatively high in PC-DM, reflecting a state of insulin resistance.
4. The pathogenesis of DM in PC is likely related to a paraneoplastic phenomenon caused by tumor secreted products. This is supported by clinical and epidemiological studies and laboratory data that supernatant from pancreatic cancer cell lines inhibits insulin secretion.

New insights on the pathogenesis of metabolic alterations in PDAC have recently emerged. Adrenomedullin, which is over-expressed in pan-

creatic cancer, was identified as a potential mediator of beta-cell dysfunction in PC-DM. Adrenomedullin is a hormone with homology semblance to amylin. Adrenomedullin receptors are found on beta cells and it is expressed in the F cells of the islets [16, 17]. Inhibition of insulin secretion in beta cells induced by supernatant from pancreatic cancer cell lines was replicated by external addition of adrenomedullin and absent by its genetic knockdown [18, 19]. Similar results were seen in orthotopic and subcutaneous in vivo tumor models using pancreatic cell lines expressing adrenomedullin [20]. Further, plasma adrenomedullin levels were higher in pancreatic cancer compared to controls and even higher levels were seen in PC-DM [20]. Overexpression of adrenomedullin was found in surgically resected specimens of pancreatic cancer [20]. These data strongly support the role of adrenomedullin for mediating diabetes in pancreatic cancer.

New-Onset Diabetes as a Harbinger of PDAC

Among the most compelling needs for PDAC research today is to develop a rational, evidence-based strategy to detect cancer at a resectable and early stage using a "DEF-C" approach: Define a high-risk group (HRG) with sixfold to eightfold higher risk of getting PDAC compared to general population; Enrich this HRG to identify a very-high risk group having 25–50 fold higher risk; and Find the lesion using an imaging modality and Confirm PDAC diagnosis with a biopsy of the lesion.

Define HRG for Sporadic PDAC: Since PDAC is relatively uncommon and often presents at an advanced stage, screening can only be effective in asymptomatic HRGs. Currently, the cohort of subjects with new-onset diabetes (NOD) over age 50 years (The NOD Cohort) is the only "actionable" HRG for PDAC. About 25% of patients with pancreatic cancer are diagnosed with DM 6 months to 36 months before the diagnosis of the cancer [12]. Conversely, subjects with NOD over age of 50 years have an eightfold higher risk for having pancreatic cancer [21]. Thus NOD may be a clue to the early detection of pancreatic cancer. However, the success of the strategy to use NOD as a marker of pancreatic cancer will depend on our ability to distinguish pancreatic cancer-associated diabetes from the more common type 2 diabetes.

Enrich HRG for Sporadic PDAC: To further enrich new-onset diabetes for PDAC, Sharma and colleagues developed the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model based on changes in weight, blood glucose, and age at onset of diabetes. The weighted scores for these 3 most discriminatory factors identify NOD subjects at high, intermediate, and very low risk of having PDAC. A score >3 in the ENDPAC model had sensitivity and specificity of 80% for PDAC. In the validation sample a model score of >3 identified 7/9 PDAC (78%) with specificity 85% while enriching PDAC prevalence 4.4-fold (3.6%). Most importantly, an ENDPAC score of <0 designated 49% of NOD as having extremely low risk for PDAC. An ENDPAC score of >3 identified 75% of PC-NOD >6 months before PDAC diagnosis [21].

Find PDAC in NOD: Using a cohort of subjects who had high-resolution scans in the pre-diagnostic phase of PDAC, Singh and colleagues determined the sensitivity of CT for pre-diagnostic PDAC and developed a PDAC CT Gram that defines the CT stages (CTs) of pre-diagnostic PDAC. CTs were abnormal in 16% and 85% at 24–36 and 3–6 months, respectively, before PDAC diagnosis. On PDAC CT Gram, an abrupt pancreatic duct cut-off/duct dilatation was seen at a median of −12.8 months; a low-density mass confined to pancreas at 9.5 months, peri-pancreatic infiltration at 5.8 months, and distant metastases only at diagnosis [22].

Efforts to Use NOD for Early Detection of PDAC

Almost all (~85%) PDAC patients have an abnormal fasting glucose and nearly half have DM, which is frequently new-onset, i.e., of <36 months duration. In a retrospectively assembled NOD

Cohort of 2122 subjects, 18 (0.85%) developed PDAC within 3 years of onset of DM, a sixfold to eightfold higher probability of being diagnosed with PDAC compared to the general population [23, 24]. In prospective screening studies in subsets of NOD, 3–14% had PDAC. Biomarker work for early detection of PDAC is currently severely limited by lack of samples from asymptomatic subjects with early stage PDAC. To address these serious impediments to early detection of PDAC, efforts are underway to assemble a prospective NOD Cohort with the goals of determining the risk of PDAC in NOD and collect biosamples from presymptomatic PDAC (Clinicaltrials.gov NCT03731637) [25]. In an ancillary study within the NOD cohort, called the Early Detection Initiative (ClinicalTrials.gov NCT04662879), subjects with NOD with an ENDPAC score >0 will be imaged with high-resolution CT scan to screen for PDAC. These studies will pave the way for utilizing a near-universal phenomenon in PDAC, glycemic disturbance, to identify the cancer early [26].

Summary

Early detection of pancreatic cancer can improve long-term survival. Strategies for early detection include identification of a high-risk group for PDAC, enrichment of the high-risk group further, and finding the lesion in the highly enriched cohort. A high-risk group has been identified in patients at least 50 years of age with new-onset diabetes. Approximately half of patients with PDAC have NOD and emerging evidence suggests that diabetes is caused by cancer. Compared to the general population, patients with NOD have sixfold to eightfold higher risk of being diagnosed with PDAC within 3 years which offers a unique opportunity for early detection. Further enrichment of the NOD group with risk prediction models could identify a very-high risk group for PDAC. Future studies should focus on understanding the pathogenesis of pancreatic cancer-associated diabetes and identifying and validating novel biomarkers and clinical risk scores that can distinguish it from type 2 diabetes.

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Pancreatic Cancer Screening

4

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Introduction

Pancreatic cancer (PC) is an aggressive disease with an increasing impact on cancer-related mortality worldwide. Prognosis has slightly improved in the last decades, with approximately 10% of patients being alive 5 years after diagnosis [1]. This disease is an unfortunate exception to the general trend of improvement in cancer-related mortality and there is a significant need for early detection and better treatment options to improve the survival and quality of life of PC patients.

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer, representing almost 90% of all reported cases [2]. Consequently, the term PC usually refers to PDAC, though it is important to acknowledge that there are also other types of malignant pancreatic tumors with different biology, prognoses, and treatments.

Pancreatic cancer is particularly challenging to diagnose, and in most cases remains "silent" until the disease has reached an advanced stage when the surgical intervention, the only potentially curative treatment is no longer an option. Five-year survival rates are influenced by the disease stage at presentation. Thus, the 5-year survival rate for metastatic disease is 2.9%, increasing to 13.3% for regional disease and 39.4% for localized disease [1]. Despite these grim statistics, there is evidence to suggest that long-term survival can be achieved in patients diagnosed at an early-stage [3–5]. Furthermore, the detection and surgical resection of precancerous lesions that give rise to invasive PDAC can potentially prevent progression to invasive cancer. Consequently, there is an increasing global interest in screening programs aimed to detect precursor lesions or PC in an early and potentially curable stage.

This book chapter will review data about risk factors and genetic predisposition for PC, will provide current information on PC precursor

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_4

lesions, and highlight current screening strategies and preliminary results.

Pancreatic Cancer Risk Factors

Several environmental and lifestyle factors have been confirmed as risk factors for PC, including cigarette smoking, alcohol consumption, diet, and high caloric intake [6, 7].

Although the increase in risk is small, PC has been linked to cigarette smoking [6]. According to several studies, the relative risk for developing pancreatic cancer among smokers is around 1.7–2.4 [8–11] but importantly, risk decreases with smoking cessation [12]. Heavy alcohol intake is a common cause of pancreatitis, which is also associated with an increased risk of PC [13].

Numerous studies have suggested a link between an increased body mass index (BMI) and PC risk [6], with a high BMI during early adulthood being associated with increased PC mortality [14]. There is also evidence that a "Western" diet (increased consumption of red or processed meat and dairy products) is associated with an increased risk for PC, although other studies have failed to identify dietary risk factors for this disease [15, 16].

Several reports have indicated an association between PC and infection with hepatitis B virus, hepatitis C virus, and Helicobacter pylori [17–19]. Chronic pancreatitis is also a well-known risk factor for PC, with one study demonstrating a 7.2-fold increased risk for PC for patients with a history of pancreatitis [20].

The association between PC and diabetes mellitus is particularly complex (see separate dedicated chapter on this topic in the book). According to a meta-analysis including 88 studies, the pooled relative risk for PC in patients with diabetes compared with non-diabetics was 2.08 (95% CI 1.87–2.32) [21]. Numerous studies have shown an association between new-onset diabetes and the development of PC, especially in elderly patients without a family history of diabetes and who experience weight loss [6]. In this scenario, diabetes is thought to be caused by cancer, although the physiologic basis for this effect is not yet completely understood. Long-term diabetes, however, seems to be a risk factor for PC as some studies have shown an association between PC and DM of 2–8 year duration [6, 22]. All the above-mentioned risk factors represent modifiable factors. By lessening or eliminating these factors, the risk of developing PC can be reduced.

While lifestyle and environmental factors are responsible for only a small proportion of PC case, aging of the population remains one of the most important factors contributing to the substantial increase in the number of PC cases observed over the last decades.

There are risk factors for PC that cannot be modified and include genetic cancer predisposition syndromes, family history of PC, non-O blood type, non-European descent [8].

An estimated 10–15% of PC cases can be attributed to genetic causes and there are two main categories of hereditary risk for PC: genetic cancer predisposition syndromes and familial pancreatic cancer (FPC) [23].

The main genetic cancer predisposition syndromes associated with an increased risk for PC are summarized in Table 4.1. Particularly high risk is reported for patients with Peutz–Jeghers syndrome, familial atypical multiple mole melanoma syndrome, and hereditary pancreatitis.

Familial pancreas cancer is defined as a family with at least two affected first-degree relatives (FDR) who do not meet criteria for a known PC-associated genetic predisposition syndrome [34]. Pancreas cancer risk is firmly linked to the number of relatives affected and their relationship. Therefore, the lifetime risk of developing PC is 8–12% (6.4×) with two affected FDR and it increases to 40% with three or more affected FDR (32×) [35]. Moreover, earlier age of onset is associated with an increased risk (kindreds with onset <50 years old have an RR = 9.3) [36].

It is important to obtain a rigorous family history when seeing a new patient with PC. In particular, a family history of pancreatitis, melanoma, pancreatic, colorectal, breast, or ovarian cancer should be noted. Patients with PC for whom a hereditary cancer syndrome is suspected should be considered for genetic counseling. All individuals, especially those with a suspicious family history should be advised on risk-reducing strate-

Table 4.1 Genetic cancer syndromes associated with an increased risk of pancreatic cancer

Syndrome	Gene(s)	Relative risk for PC	References
Peutz–Jeghers syndrome	STK11	132-fold	[24]
Familial atypical multiple mole melanoma syndrome	CDKN2A	22-fold, 46.6-fold	[25, 26]
Hereditary breast/ovarian cancer	BRCA1	2.6-fold; 3-fold	[27] [28, 29]
	BRCA 2	21.5-fold; 6.2-fold; 8.9-fold	[30] [28] [29]
	PALB2	2.7-fold	[28]
Lynch II syndrome	Mismatch repair genes MLH1, MSH2, MSH6	8.6-fold	[31]
Hereditary pancreatitis	PRSS1, SPINK1	53-fold; 87-fold	[32, 33]
Ataxia telangiectasia (ATM)	ATM	6.2-fold; 8.8-fold	[28, 29]
Li-Fraumeni	(TP53)	8.3-fold; 7.1-fold	[28, 29]

PC pancreatic cancer

gies including smoking cessation and weight loss.

Pancreatic Cancer Precursor Lesions

There has been progress in characterizing the precursor lesions that give rise to invasive PC: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs).

Most of the PCs arise in a stepwise manner from PanINs. These lesions are graded as low (PanIN-1), intermediate (PanIN-2), or high (PanIN-3) grade based on their degree of cellular and nuclear atypia [37]. Molecular studies have demonstrated an accumulation of genetic alterations as PanINs progress towards PDAC, with early mutations in KRAS followed by alterations in CDKN2A, TP53, and SMAD4 among others [38]. Typically, PanINs are microscopic and therefore difficult to find on imaging during screening. However, studies have shown that when premalignant lesions are resected before developing invasive features, it results in a 5-year survival rate up to 85% [5].

IPMNs and MCNs are responsible for about 15–30% of PCs [6]. These are cystic lesions and therefore can be radiologically detected. IPMNs are cystic epithelial neoplasms characterized by papillary projections and mucin production that can be found in the main pancreatic duct or its side branches [37]. The risk of malignant transformation for IPMN has been found to range from 19% to 60%, with main-duct types having the highest risk [39]. IPMNs can also be associated with the phenomenon of field cancerization (also called a "field defect") whereby the growth of one IPMN indicates that cancerous lesions may arise in other areas of the pancreas [40].

Rarely, mucinous cystic neoplasms (MCNs), which are slow growing cystic tumors that are usually found in women, may develop into PDACs, though the malignant potential of MCNs is not clear [41]. Unlike IPMNs, MCNs are not associated with field cancerization and their resection leads to a 5-year survival rate of nearly 100% [42].

Despite a growing understanding of PC precursor lesions, only 15–20% of PC is surgically resectable at time of diagnosis due to a current lack of effective, population-wide screening tests that can identify early-stage disease.

Who Should Be Screened?

Pancreatic cancer has an overall low incidence (lifetime risk 1.6) [1] and therefore it is not cost-effective to screen the general population. However, selective screening of high-risk individuals is considered beneficial.

The International Cancer of the Pancreas Screening (CAPS) Consortium published updated consensus criteria for screening individuals based upon their genetic susceptibility or family history [43]. The worldwide experts recommend that all patients with Peutz–Jeghers syndrome and all carriers of germline CDKN2A

mutation should be screened for pancreatic cancer regardless of family history, starting at age 40. Carriers of BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2, or MSH6 germline mutations with at least one affected FDR should be screened as well, starting at age 45 or 50, or at 10 years younger than the youngest affected blood relative. Individuals without mutations in pancreatic cancer susceptibility gene, but with at least one affected FDR and one affected second-degree relative on the same side of the family are also considered candidates for high-risk pancreatic cancer screening, starting at age 50 or 55 or at 10 years younger than the youngest affected blood relative.

There is also data to suggest that patients with new-onset diabetes but without traditional risk factors for diabetes (e.g. metabolic syndrome) are also at increased risk for pancreatic cancer and could potentially benefit from screening [44–46].

The MD Anderson Pancreatic Cancer High-Risk Clinic currently performs surveillance based on risk stratification following the most recent NCCN guidelines [6, 47]. Patients who meet the eligibility criteria are enrolled in a program which includes annual contrast-enhanced MRI/MRCP and/or EUS.

Screening Tests

None of the current modalities currently used for PC diagnosis has all the attributes requirements for an effective screening tool. The development of a non-invasive, cost-effective, sensitive, and specific screening test is crucial for decreasing mortality from PC.

Most screening programs rely on endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) [23]. Studies comparing EUS, MRI, and CT demonstrated similar frequent detection of pancreatic lesions by EUS and MRI, compared with CT. EUS and MRI have been shown to be complementary in one prospective, blinded study [48]. EUS has the ability to detect small pancreatic lesions and it also can identify subtle non-specific parenchymal abnormalities, which in a high-risk setting may represent the effects of PanIN with associated lobulocentric atrophy [49, 50]. Moreover, EUS offers the possibility of tissue sampling through fine-needle aspiration/biopsy (FNA/FNB) in case of suspicious lesions [46].

The role of CA19–9 testing has not been studied in high-risk individuals, however its diagnostic performance in patients with PC has been well-documented [43, 51]. Accordingly, there was consensus that CA19–9 testing should be performed when there is concern about the possibility of pancreatic cancer, such as when worrisome features are found on pancreatic imaging. Experts also reached consensus that glucose testing (fasting glucose or HbA1C) to detect new-onset diabetes was reasonable for high-risk individuals [43].

Screening Guidelines and Strategies

The CAPS consortium guidelines recommend screening at baseline with EUS plus MRI/MRCP, along with fasting blood glucose and/or HbA1c. For patients with normal baseline examination findings, the recommendation is to alternate MRI/MRCP plus EUS on an annual basis with fasting blood glucose or HbA1c [43]. The age for stopping screening is individualized based on each patient's medical status (eligibility for surgical treatment of detected lesions), life expectancy, and preference.

The American Society of Clinical Oncology (ASCO) also provided guidelines on which individuals should be screened based on genetic and familial risk [52]. They recommended that germline genetic testing should be offered to patients with PC after discussion of risks and benefits, to determine familial predisposition and identify the need for PC surveillance.

It is critically important to recognize that up to 40% of PDAC patients who harbor germline mutations that could lead to the development of pancreatic cancer (such as BRCA1/2 mutations) exhibit no significant family history of breast,

ovarian, prostate, or pancreatic cancer. For this reason, the National Comprehensive Cancer Network (NCCN) guidelines now recommend that all pancreatic cancer patients undergo germline testing for an inherited mutation [6, 47]. In line with the CAPS and the NCCN, ASCO recommends that PC screening should be performed at centers with appropriate expertise in managing individuals with PC risk.

The European Society of Gastrointestinal Endoscopy (ESGE) recently published a position statement regarding the role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe [46]. For PC screening, ESGE recommends that EUS may be used in selected high-risk patients, such as those with a strong family history and/or genetic susceptibility. Given the evolving nature of this field, screening for PC should preferably be performed within a research setting, or at referral centers with dedicated EUS experts with clinical expertise and interest in this field, in the context of a multidisciplinary high-risk screening program.

The United States Preventive Service Task Force (USPSTF) published and reaffirmed its decision to provide a Grade "D" recommendation for PC screening in asymptomatic, average-risk individuals [53]. Although the USPSTF maintained its "do not screen" recommendation for asymptomatic adults because of the lack of evidence, it indicated that "this recommendation does not apply to these high-risk populations."

MD ANDERSON Screening Algorithm

Patients who meet the eligibility criteria (Table 4.2) are enrolled in a screening program which includes annual contrast-enhanced MRI/MRCP and/or EUS. For patients considered to be at high risk for pancreatic cancer, we currently alternate MRI and EUS. For patients with worrisome features on these investigations, screening intervals can be shorter, based on clinical judgment. Small cystic lesions identified on screening do not require any further intervention and are usually followed [47].

Table 4.2 Eligibility criteria for pancreatic cancer screening

Risk factors	Eligibility
Family history of PC	≥ 2 FDR from the same side of the family with PC ≥ 3 FDR and/or SDR from the same side of the family with PC
STK11 germline mutation (Peutz–Jeghers syndrome)	Irrespective of family history
CDKN2A germline mutation	
PRSS1 mutations and hereditary pancreatitis	
BRCA1/2 mutation	Germline mutation + family history of PC (FDR or SDR on the same side of the family as the germline variant)
MLH1, MSH2, MSH6, EPCAM mutations	
PALB2 or ATM mutations	
TP53 mutations	

PC pancreatic cancer, *FDR* first-degree relative, *SDR* second-degree relative

Benefits and Harms

Over the last 20 years multiple centers in Europe and the USA have developed pancreatic screening programs. Recent encouraging data regarding impact of PC screening on survival has been published. A study by Canto et al. [54] aimed to determine the incidence of neoplastic progression in 354 high-risk individuals enrolled in various cohorts across the USA from 1998 through 2014. Results showed that neoplastic progression occurred in 7% of the individuals enrolled in screening programs and 85% of the patients survived for 3 years. This is a critical advance because it suggests that downstaging, and therefore real benefit of screening, is possible. Furthermore, screening high-risk individuals can detect PC with a high resectability rate. Thus, in a cohort of screen-detected pancreatic cancers, the 1-year and 5-year survival rates were 90% and 60%, respectively [55]. Surgical treatment was associated with a relatively short length of stay and low readmission rate, acceptable morbidity, and zero 90-day mortality. Similarly, surgical resection of detected PC was associated

with zero perioperative mortality and acceptable morbidity in patients prospectively followed in three expert European centers [56].

There are substantial challenges when it comes to PC screening. The disease is rare and the prevalence of PC in asymptomatic patients is therefore very low. Even an extremely specific screening test (99% specificity) poses the risk of false positive results when applied to the general population. The false positive results will increase patients' anxiety and lead to additional testing and perhaps even unneeded surgery. However, although pancreatic cancer is relatively rare, populations with a significantly increased risk have been identified and are now targeted for screening.

Screening can lead to surgical interventions of uncertain benefit, which may include the resection of benign/low risk lesions or tumors that are already metastatic. With current technology it is often impossible to distinguish between pancreatic precursors that harbor either early cancer or high-grade dysplasia and low-grade precursors that can be safely watched. Thus, up to 60% of patients who undergo surgical resection for a precursor lesion are found to have a lesion with a low risk of progression and not to require surgery at the time [57, 58].

It is important to acknowledge that some patients who are diagnosed with early-stage disease and undergo an R0 resection may still have rapid progression of disease. Earlier detection does not protect against poor tumor biology and may instead afford a slight increase in lead time before death (rather than true increased survival).

Possible complications of the screening process include procedure-related complications such as the administration of intravenous contrast, EUS-FNA, and anesthesia-related complications. MRI and EUS have been recognized as the screening modalities with the most favorable risk/benefit characteristic.

Psychological Impact of Pancreatic Cancer Screening

Participation in a screening program has the potential to increase patient anxiety related to the development of cancer. Our group conducted a systematic review that addressed the psychological aspects of PC screening [59] and included six cohort studies and one cross-sectional study that addressed the psychological aspects of PC screening. Overall, studies have demonstrated the absence of an increase in risk perception and cancer worry, and participation may reduce anxiety in some patients [60, 61]. Although screening might not always be reassuring, it may improve individuals' quality of life, and this should be an important aspect when considering PC screening. Moreover, to cope with anxiety, it would be useful for patients to be in contact with professionals and rely on recent medical progress in this evolving field.

Another approach to evaluate the benefits of pancreatic cancer screening would be to consider its impact on the quality of life (QOL) of the individuals who are at risk for developing cancer. Our group has also conducted a study to clarify the psychological impact of EUS in patients with pancreatic cystic lesions (PCLs) and individuals at risk for developing PC [62]. The hypothesis was that a benign EUS exam in these patients may result in less distress and improved QOL. Participants were administered the brief profile of mood states (POMS) and the single-item linear analog scale assessment (LASA) quality of life (QOL). The questionnaires were chosen based on their known psychometric properties and clinical usefulness in evaluating distress and overall QOL. Participants were asked to complete the questionnaires regarding their pre- and post-EUS status for distress and QOL. Forty patients were included in the study: 17 patients underwent EUS for evaluation of a known PCL and 23 patients were at high risk for developing PC based on their familial and/or genetic background and they underwent EUS as part of a PC screening program. There was a significant difference in patients' overall QOL assessed by the LASA QOL scale before and after the EUS procedure (mean difference 0.73, SD 1.76, $p < 0.01$). Similarly, a significant difference in the brief POMS score was found before and after the EUS procedure (mean difference −5.46, SD -6.72, $p < 0.01$).

Thus, the impact of EUS (or MRI) screening on survival is beginning to emerge [54, 55], and

additionally there may be a psychological benefit that clinicians should be aware of when considering screening for pancreatic cancer in high-risk patients. Conversely, further studies should be done to assess for possible psychological harm when precursor lesions or false positive findings are detected during screening.

Future Directions

Further data is required to evaluate the effectiveness and outcomes of PC screening in settings outside of high-volume academic centers and clinical trials. Furthermore, active research is aiming to improve the efficacy of current screening modalities, but also to develop new biomarkers accurate enough for population-wide screening.

An emerging promising approach is the fusion of artificial intelligence (AI) methods with imaging in PC screening and risk stratification. Therefore, lesions that are not detectable or missed now could in the future be detected automatically by novel deep learning approaches running in the background as scans are generated. There is already evidence to suggest that augmentation of EUS images with AI can improve the diagnosis of malignant lesions [63, 64]. Furthermore, an artificial neural network approach was used to analyze personal health data and was found to predict PC with a sensitivity and specificity as high as 87.3% and 80.8% based on health biometrics alone [65].

There is a need to further refine screening strategies and include non-imaging-based biomarkers. Emerging data suggest the potential of circulating tumor DNA (ctDNA), microRNAs (miRNAs), or exosomes for detection of PC, even in a general non-high-risk population [8, 66].

Conclusions

Multiple centers across the world have developed PC screening programs for patients at high-risk for developing PC with the aim to identify early invasive PC and precursor lesions. There is limited data suggesting that screening may improve survival. The risks associated with screening include procedure-related complications, overdiagnosis, and false positive results. Screening for PC should preferably be performed in the setting of a research protocol at an experienced center or in the setting of a multidisciplinary team.

Early detection of PC is a challenging task; however, there are key opportunities on the horizon that will improve the profile of potential benefits and harms from screening and will refine the current understanding of the ideal patient population for screening.

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Part I

Diagnosis and Staging of Pancreatic Cancer

5 Diagnosis and Staging of Pancreatic Cancer: Imaging Evaluations—Pancreatic Protocol CT and MRI, PET-CT

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Computed Tomography

Computed tomography (CT) is the imaging modality of choice for detection and staging of pancreatic cancer due to its high spatial resolution and the ability to produce multiplanar reformats. The proper imaging protocol and technique is crucial for these purposes.

CT Protocol

Recent recommendations from the National Comprehensive Cancer Network, based on consensus publications written by members of the American Pancreatic Association including radiologists from the Society of Abdominal Radiology, provide detailed instructions to optimize imaging with computed tomography [1]. These recommendations include the following for a CT examination optimized for detection, characterization, and staging of a pancreatic mass that may be a pancreatic tumor. Intravenous iodinated contrast should be injected rapidly at a rate of approximately 3–5 mL per second. Imaging should be obtained during the phase of peak pancreatic parenchymal enhancement, typically 40–50 s following the start of injection of intravenous contrast, followed then by a second phase, a portal venous phase, at 65–70 s after the start of contrast injection. The pancreatic parenchymal phase facilitates imaging of the primary tumor, as well as arterial anatomy, while the portal venous phase facilitates visualization of venous structures and the detection of liver metastases. Neutral contrast, such as water, should be utilized. Images should be obtained at the thinnest slice profile possible, preferably submillimeter, to allow for reconstructions in the axial, coronal, and sagittal planes at a 2–3 mm slice thickness to facilitate visualization of the relationship of tumor to vessels (Fig. 5.1). Dual energy imaging techniques, in which X-ray beams of two different energies are utilized at the same time, have been shown to improve the visibility of pancreatic tumors, particularly low, 40–50 keV monochromatic energy images as well as iodine material density images which empha-

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_5

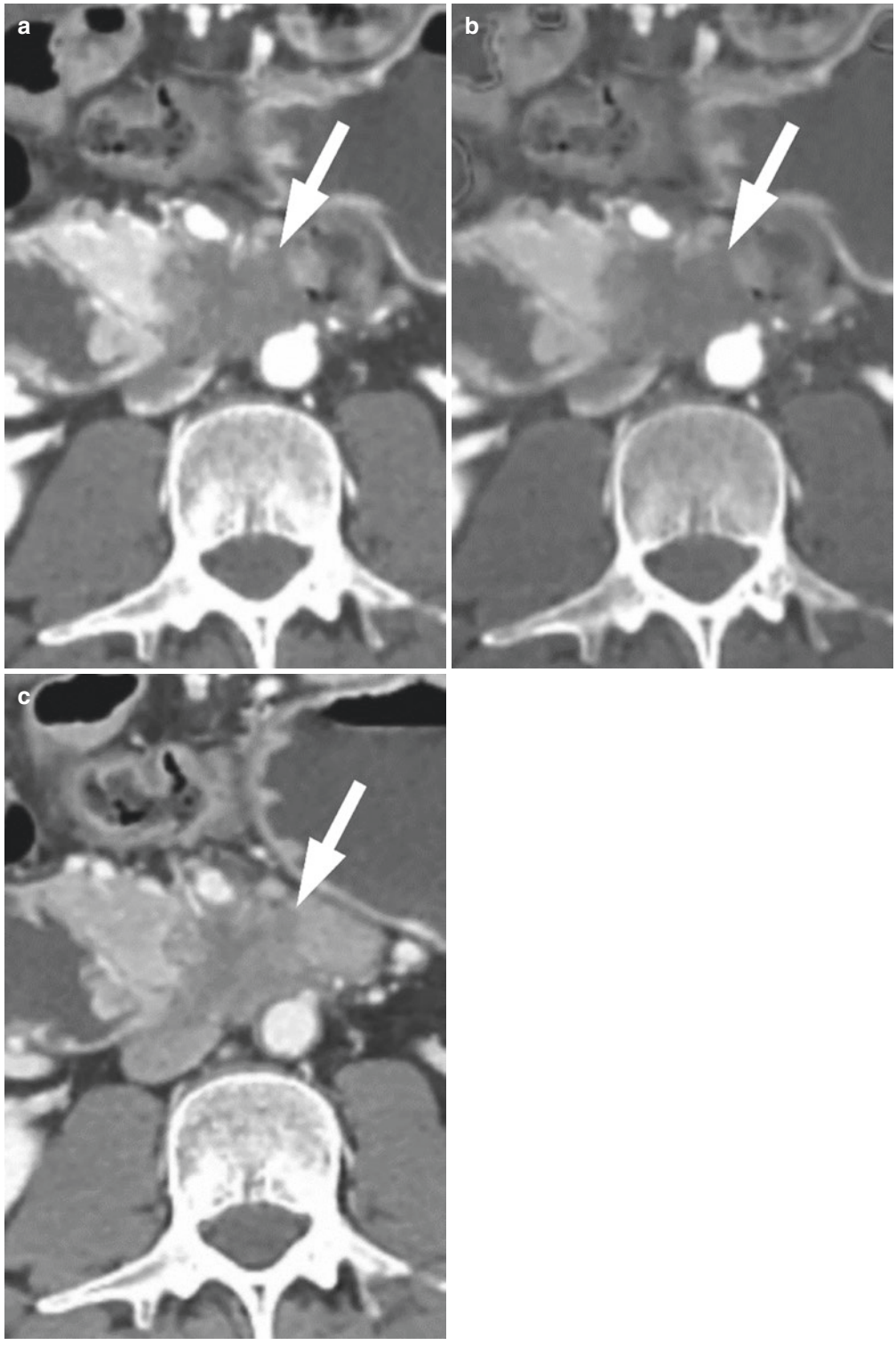

Fig. 5.1 Pancreatic head mass (white arrow) as seen on the (**a**) late arterial phase, (**b**) late arterial phase on an iodine material density dual energy image, and (**c**) late arterial phase. Note how boundaries of tumor and difference between tumors are better seen on late arterial phase and particularly the iodine material density image

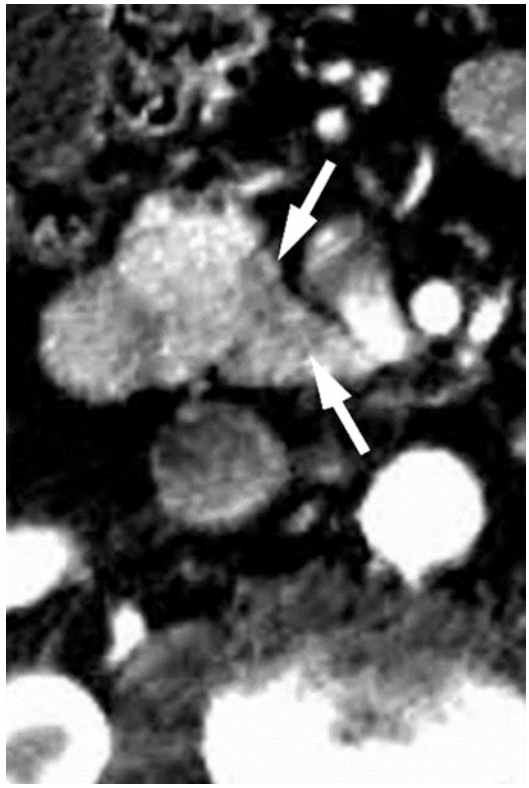

Fig. 5.2 Medial hypodense pancreatic head lesion (white arrows), biopsy proven chronic pancreatitis. Lesion remained stable over the course of multiple examinations

size the presence of iodinated contrast (Fig. 5.1) [2, 3]. Alternatively, imaging can be done using a low kVp (80-100kVp) technique to improve contrast, though limitations on tube output may constrain imaging with regard to patient size [4, 5].

Diagnosis

Pancreatic ductal adenocarcinoma (PDAC) on contrast-enhanced CT typically has the appearance of a solid mass. This is variably hypodense to background pancreas on the pancreatic parenchymal phase of enhancement (late arterial phase) (Fig. 5.1). The sensitivity for the detection of tumor on multidetector CT has been reported to be approximately 86–97% when considering tumors of all sizes, but decreases to a sensitivity of 77% for tumors under 2 cm [6–9]. Dual energy imaging techniques have been shown to improve the conspicuity of primary tumors, particularly low keV monochromatic energy images, approximately 40–50 keV, and iodine material density images, the latter emphasizing the differences in contrast enhancement between tumor and background pancreas [2, 3]. However, even with biphasic imaging, pancreatic tumors can be isodense to the background pancreas. A study utilizing multidetector CT noted an incidence of 11% for isoattenuating tumors even during the phase of peak pancreatic enhancement [10].

In the case of such isoattenuating tumors, it is important to be aware of secondary signs, which may be the only indicator(s) present. These include atrophic pancreatic parenchyma within the upstream pancreas, abnormal mass effect including regional pancreatic enlargement, abnormal pancreatic contour, and abnormalities of the pancreatic and/or common bile duct. Abnormalities of the main pancreatic duct include an interrupted or obstructed main pancreatic duct [10]. Studies have shown that dilatation of the main pancreatic duct with cut-off can be seen in nearly half of cases as distant as 2–18 months prior to establishing a clinical diagnosis of pancreatic cancer [11].

Differential Diagnosis

One of the challenges is the broad differential diagnosis for a hypodense or isodense pancreatic mass, the primary concern always being the possibility of pancreatic ductal adenocarcinoma. For this reason, tissue sampling is almost always needed to guide further management. The etiologies that will be covered include both inflammatory and neoplastic.

The primary inflammatory considerations are forms of chronic pancreatitis, both conventional and autoimmune varieties. Histopathologically, conventional (non-autoimmune) chronic pancreatitis is characterized by parenchymal destruction with replacement by fibrotic tissue classically resulting in an atrophied pancreas [12, 13]. However, chronic pancreatitis can also manifest as a focal mass (30%) (Fig. 5.2) causing features that mimic pancreatic ductal adenocarcinoma, including duct obstruction [13, 14]. Overall, CT

has been reported to have a specificity of only 70% when discriminating between mass-forming chronic pancreatitis and pancreatic ductal adenocarcinoma [15]. Another challenge is that patients with chronic pancreatitis are at risk for developing pancreatic ductal adenocarcinoma [16]. For this reason, even if a biopsy of such a mass is negative for malignancy and is indicative of pancreatitis, close observation, and consideration for re-biopsy is adviased because of the issues like smapling errors and potenrial future development of cancer.

Autoimmune pancreatitis, a manifestation of a related systemic disease, has an average age of onset of 60 years, but can affect a wide age range [17]. It manifests as two main types: Type 1, a predominantly lobular inflammatory manifestation with a typically diffuse fusiform appearance in which most patients develop an elevated serum IgG4 level, and Type 2, histopathologically associated with granulomas centered about ducts, commonly forming a mass, and only rarely mounting an elevated serum IgG4 level [17].

The neoplastic differential diagnosis for pancreatic ductal adenocarcinoma includes primary and metastatic tumors.

Primary pancreatic neuroendocrine tumors, while classically hyperenhancing on the pancreatic parenchymal phase, can be isoenhancing or even hypoenhancing on the pancreatic parenchymal phase; hypoenhancing variants were also identified to have poorer prognosis with higher rates of nodal and liver metastases [18].

Primary pancreatic lymphoma is rare, but secondary pancreatic involvement has been reported in up to 30% of cases of non-Hodgkin lymphoma [19]. The appearance can be variable, including diffuse pancreatic involvement as well as manifesting as one or more solid masses (Fig. 5.3), with or without obstruction of the main pancreatic duct [19].

Several extra-pancreatic primary tumors can metastasize to the pancreas. These include those originating in the breast, colon (Fig. 5.4), kidneys, lungs, and prostate. Sarcomas, melanoma, and bowel carcinoid tumors can also metastasize to the pancreas. These lesions can show a variety of enhancement patterns, ranging from hyper- to hypoenhancement. While the presence of multiple solid lesions is a useful indicator for metastatic disease or lymphoma, metastatic disease to the pancreas can often manifest as a solitary lesion. For this reason, the possibility of metastatic disease, rather than solely primary pancreatic cancer, should be considered in the setting of a known extra-pancreatic primary. Biopsy and tools such as immunohistochemistry are often helpful.

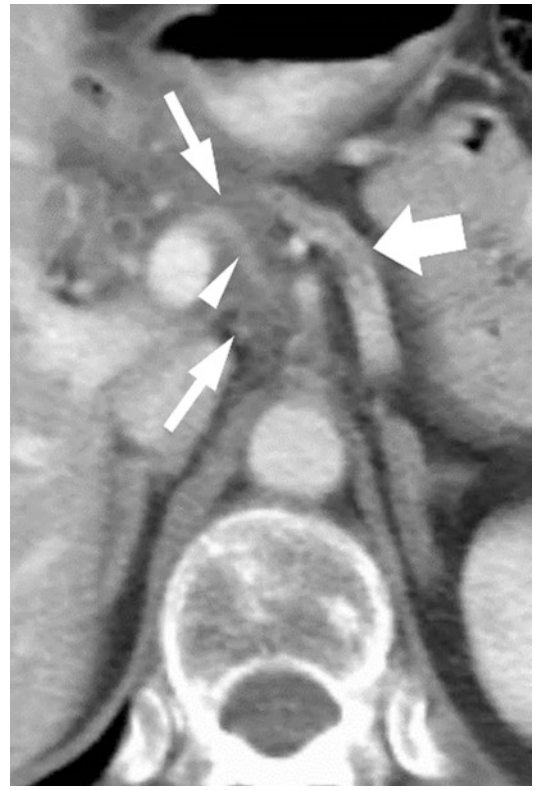

Fig. 5.3 Pancreatic neck hypodense mass (white arrows), confirmed as lymphoma, encasing the common hepatic artery (white arrowhead). Atrophic upstream pancreas (thick white arrow)

Staging

The American Joint Committee on Cancer (AJCC) provides staging criteria for pancreatic adenocarcinoma that follows the tumor/node/metastasis (TNM) model. There are criteria within the TNM model that can only be obtained

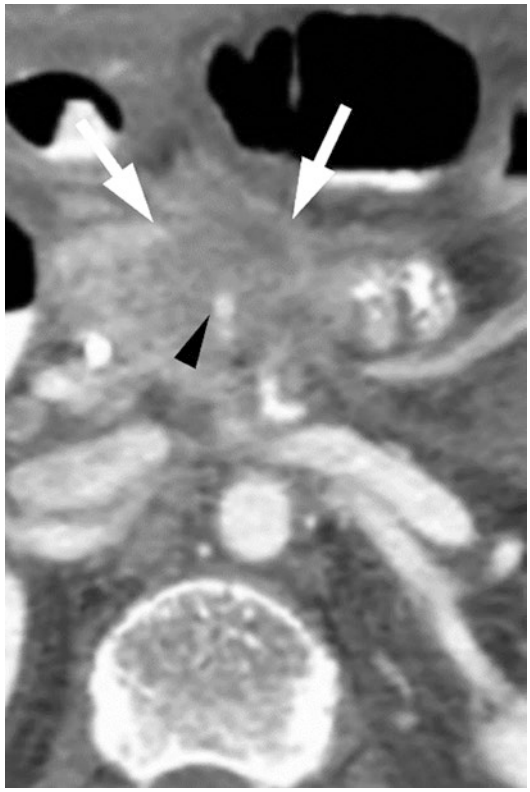

Fig. 5.4 Metastatic colon cancer mass (white arrows) involving the pancreatic head and central mesenteric vessels, with 360° encasement of the superior mesenteric artery (black arrowhead)

after surgery, for example, nodal staging. Thus, the TNM system is more tailored for stratification and prognostication rather than pre-operative evaluation. In 2016, the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual was released which included updates on the staging of pancreatic cancer (Table 5.1). One important change was splitting pancreatic cancers into cancers of the endocrine pancreas and exocrine pancreas, which now use different staging systems. Primary tumor staging (T) was moved from a more descriptive-based to a more size-based system. Nodal staging (N) was changed to incorporate the number of positive lymph nodes.

T-staging is divided into four categories, T1–T4, based on tumor size and involvement of the celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA). A T1 tumor is defined as a tumor size ≤2 cm without involvement of the CA, SMA, or CHA. The eighth edition of the AJCC staging manual has further subcategorized T1 into T1a (tumor ≤0.5 cm), T1b (tumor >0.5 and < 1 cm), and T1c (tumor 1–2 cm). A T2 tumor is defined as a tumor >2 cm and ≤ 4 cm in greatest dimension without involvement of the CA, SMA, or CHA. A T3 tumor is defined as a tumor >4 cm without involvement of the CA, SMA, or CHA. Previously in the seventh edition of the AJCC Staging Manual, the T3 category was defined as a tumor that extends beyond the pancreas, regardless of size, but without involvement of the celiac axis or the superior mesenteric artery. However, extension beyond the pancreas may vary among pathologists and may not be reproducible. Additionally, the pancreas lacks a true capsule to delineate extension beyond the pancreas, and chronic pancreatitis can obliterate the pancreatic and peripancreatic interface which can contribute to difficulty in determining extension beyond the pancreas [20]. As a result, nearly all cases of PDAC could be classified as T3 disease based on extra-pancreatic according to the seventh edition [21]. The T4 category is assigned to tumors that involve the celiac axis, superior mesenteric artery, or common hepatic artery, regardless of size. One change in the definition of a T4 tumor between the seventh and eighth editions is removal of the phrase "unresectable primary tumor" because resectability varies among institutions.

N-staging is divided into three categories. N0 refers to no regional lymph node metastasis. N1 is defined as metastasis to 1 to 3 regional lymph nodes. N2 is defined as metastasis to 4 or more regional lymph nodes. N-staging was changed to incorporate the number of positive lymph nodes which has shown better prognostication for survival. In one study, 5 year survival rates for N0 status were 35.6%, N1 status was 20.8%, and N2 status was 10.9% ($P < 0.01$) [22].

M-staging remains unchanged between the seventh and eighth editions. M0 is defined as no distant metastases are present. M1 is defined as distant metastases are present.

To address tumor resectability, there are different classification systems from different insti-

Table 5.1 American Joint Committee on Cancer (AJCC) Staging Manual for pancreatic cancer comparing seventh and eighth editions

	AJCC Staging Manual (seventh edition, 2010)	AJCC Staging Manual (eighth edition, 2016)
Primary tumor (T)	**TX** primary tumor cannot be assessed	**TX** primary tumor cannot be assessed
	Tis carcinoma in situ	**Tis** carcinoma in situ
	T1 tumor limited to the pancreas, ≤2 cm in greatest dimension	**T1** tumor ≤2 cm in greatest dimension **T1a** tumor ≤0.5 cm in greatest dimension **T1b t**umor > 0.5 and < 1 cm in greatest dimension **T1c** tumor 1–2 cm in greatest dimension
	T2 tumor limited to the pancreas, >2 cm in greatest dimension	**T2** tumor >2 cm and ≤ 4 cm in greatest dimension
	T3 tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	**T3** tumor >4 cm in greatest dimension
	T4 tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	**T4** tumor involves celiac axis, superior mesenteric artery, or common hepatic artery, regardless of size
Node status (N)	**NX** regional lymph nodes cannot be assessed	**NX** regional lymph nodes cannot be assessed
	N0 no regional lymph node metastasis	**N0** no regional lymph node metastasis
	N1 metastasis to regional nodes	**N1** metastasis to 1 to 3 regional nodes
		N2 metastasis to 4 or more regional nodes
Distant metastasis (M)	**M0** no distant metastasis present	**M0** no distant metastasis present
	M1 distant metastasis present	**M1** distant metastasis present

Table 5.2 Comparison of resectability across different organizations

Vascular Involvement	NCCN 2019	MDACC	AHPBA/SSAT/SSO
SMA ≤ 180°	Borderline	Borderline	Borderline
SMA > 180°	Unresectable	Unresectable	Unresectable
CA ≤ 180°	Borderline	Borderline	Unresectable
CA > 180°	Head/uncinate: Unresectable Body/tail: Borderline if aorta and GDA uninvolved to allow for modified Appleby procedure	Unresectable	Unresectable
CHA abutment or short segment encasement	Borderline	Borderline	Borderline
PV or SMV > 180° or ≤ 180° with contour irregularity or thrombosis with reconstruction possible	Borderline	Borderline	Borderline

tutions and societies. MD Anderson Cancer Center (MDACC) was the first to publish such a system [23]. Other classifications include the National Comprehensive Cancer Network (NCCN), as well as the joint consensus between the Americas Hepato-Pancreato-Biliary Association (AHPBA), Society for Surgical Oncology (SSO), and Society for Surgery of the Alimentary Tract (SSAT). Common to the classification systems, pancreatic adenocarcinoma can be categorized as resectable, borderline resectable, and unresectable based on the presence or absence of distant metastatic disease and degree of artery and vein involvement by the tumor. These differences are highlighted in (Table 5.2).

The degree of vascular involvement of tumor is based on how much of the tumor contacts the surface of the involved vessel, from no contact to 360 degrees. This can be divided into tumors that have ≤180° of contact with the vessel (abutment) and >180° of contact with the vessel (encasement). One prospective study evaluated the degree of vascular involvement on pre-operative CT in 25 patients who underwent resection or palliative surgery for PDAC. The authors found that >180° of involvement had a positive predictive value of 95% and negative predictive value of 92% for unresectability of the tumor from the vessel [24]. Deformities in the involved vessels such as a tear-drop deformity are other qualitative factors that help determine vascular involvement. A tear-drop deformity describes the shape of the vessel as it is pinched by the surrounding tumor which is indicative of vascular invasion regardless of the degree of tumor-vessel contact [24–26] (Fig. 5.5).

Resectable tumors are those without arterial tumor contact of the CA, SMA, or CHA, or venous tumor contact of the PV, SMV, or ≤180° of involvement without venous contour deformity (Fig. 5.6).

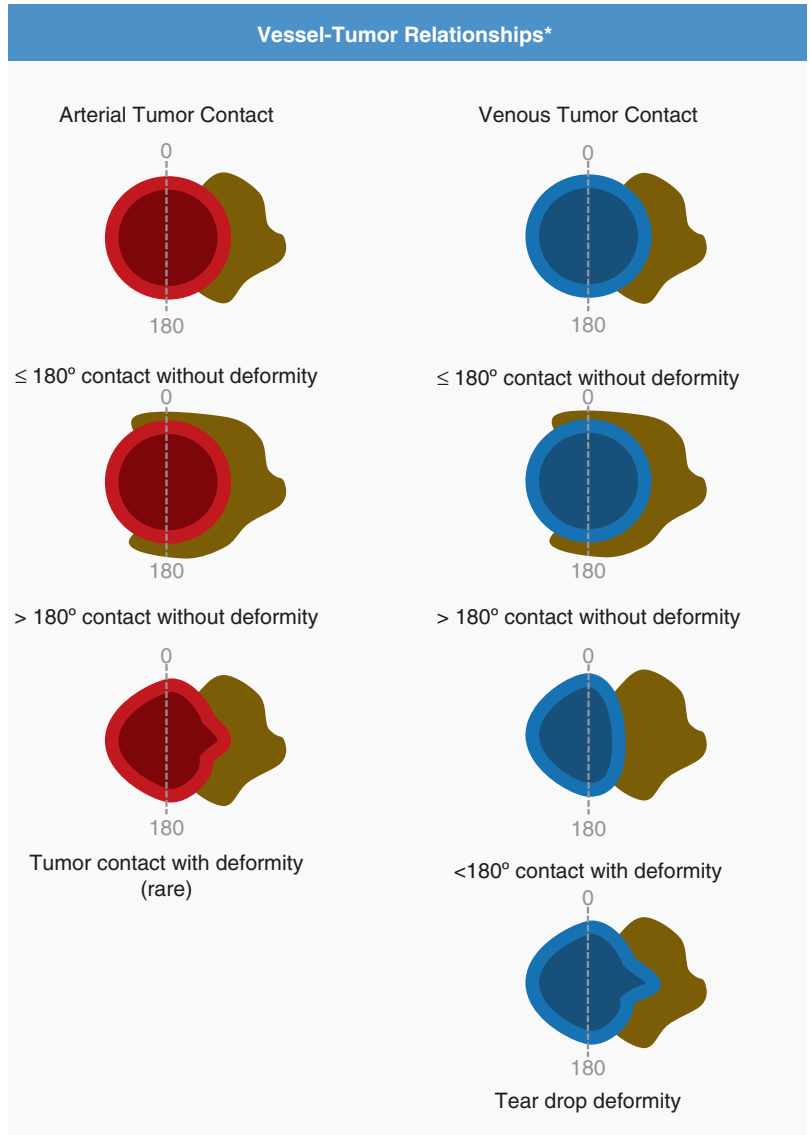

Fig. 5.5 The degree of vascular involvement of tumor, based on how much of the tumor contacts the surface of the involved vessel (0–360°) [26]

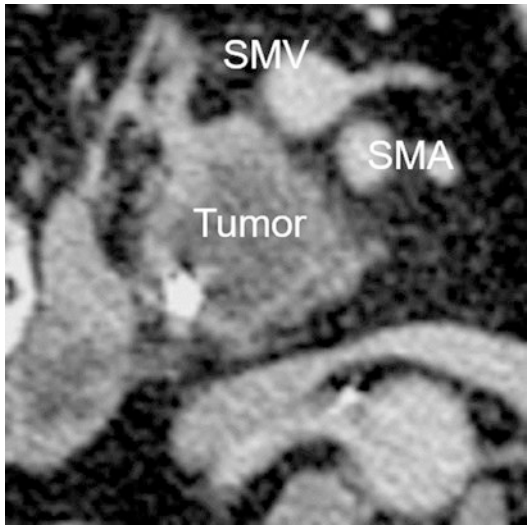

Fig. 5.6 The SMV and SMA are uninvolved by the pancreatic cancer. There is a clear fat plane between these vessels and the tumor, qualifying this as a resectable mass

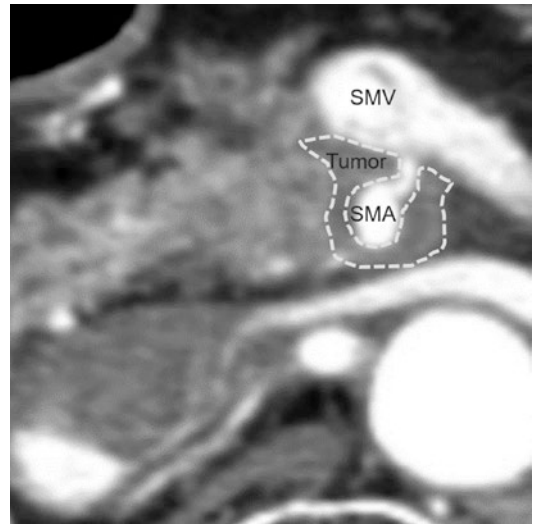

Fig. 5.7 The tumor contacts >180° of the SMA qualifying this as an unresectable mass

Unresectable tumors are those with distant metastatic disease including non-regional lymph node metastasis or locally advanced disease. Tumors involving >180° degrees of the CA or SMA are unresectable, as are those with venous involvement that do not allow for vascular reconstruction, or contact with the most proximal draining jejunal branch into the SMV (Fig. 5.7). AHPBA/SSAT/SSO guidelines define any tumor abutment (≤180°) of the CA as unresectable.

Borderline resectable masses are those that have degrees of vascular involvement that fall in between the definition of resectable and unresectable disease. Tumors that show >180° of involvement of the SMV or PV, or those with ≤180° of involvement with contour abnormality that are reconstructable are considered borderline resectable. Tumors that contact ≤180° or with short segment encasement (>180°) of the CHA or contact ≤180° of the SMA are also borderline resectable (Fig. 5.8).

For borderline resectable tumors that undergo pre-operative therapy with chemotherapy or radiation, it is important to note that radiologic downstaging is rare after treatment. The imaging appearance of the tumor before treatment and

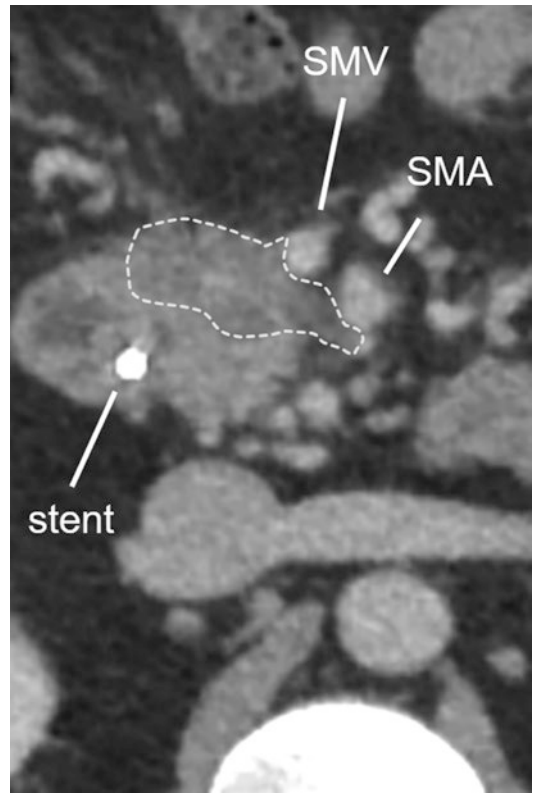

Fig. 5.8 The tumor contacts ≤180° of the SMA and SMV, qualifying this as a borderline resectable mass

after treatment is unlikely to change based on RECIST criteria or alter the imaging appearance of vascular involvement. In a study by Katz et al. that evaluated borderline PDAC after neoadjuvant therapy, only 1 out of 129 patients showed a radiographic reduction in vascular involvement to improve their anatomic stage, while 15 out of 122 patients met criteria for treatment response by RECIST criteria. Despite the findings, R0 (margin-negative) resection was achieved in 81 out of the 101 patients that did not develop metastatic disease [27]. The median overall survival between patients that did not show a radiographic response to therapy was the same as those that did show a radiographic response [27].

The use of standardized reports and standardized language for pre-operative staging CT provides consistency for crucial information that helps to determine optimal management, as well as improve patient care across institutions. Standardized reports should include morphologic, arterial, venous, and extra-pancreatic findings. Under morphologic findings, one may describe tumor location (head, uncinated process, body, tail), size, appearance, pancreatic ductal and biliary ductal dilation. Arterial findings should include variant arterial anatomy, assessment of the CA, CHA, and SMA, and evaluation for soft tissue contact, hazy attenuation or stranding, vessel narrowing or contour abnormality. Venous findings should include assessment of the portal vein and SMV, documentation of thrombus and collaterals, and vessel narrowing or contour abnormality. Extra-pancreatic findings should include evaluation of nodes, liver lesions, peritoneal disease, ascites, and other sites of metastatic disease.

Positron Emission Tomography/ Computed Tomography

Positron emission tomography/computed tomography (PET/CT) imaging has been used to diagnose, stage, and follow up of pancreatic cancer. PET imaging uses the principle of tumor glycolysis to detect sites of disease and has been used as a prognostic indicator. PET/CT integrates both, morphological and functional data, to compensate for some deficiencies from individual modalities (poor contrast resolution on CT imaging for small lesions and poor spatial resolution in PET imaging). Since the normal pancreas is not highly metabolic on PET, any region of increased radiotracer uptake should be considered abnormal.

PET/CT Protocol

The radiopharmaceutical tracer used in the diagnosis and management of the great majority of malignancies is 18-F-FDG (18-F-fluoro-2-deoxyglucose) which is administered intravenously; therefore, intravenous (IV) access must be obtained prior to examination. Dosage recommended by the International Commission on Radiological Protection (ICRP) is approximately 259 MBq (7 mCi) of FDG with variability between 290 s and 500 s MBq (8–15 mCi) in an adult patient [28, 29]. Since 18-F-FDG is an analog of glucose, 6–8 h of fasting is recommended prior to the examination. The blood glucose levels are tested and should be within normal limits (4–7 mmol/L) or at least less than 140 mg/dL. Patients are usually placed in a dark quiet room prior to the examination to limit physiologic uptake in the muscles. Once the tracer is injected, it has an initial physiologic distribution into the brain, heart, kidneys, and urinary tract within 60 min. Imaging is acquired 60 min post-injection. The images are acquired from head to toe, first with low dose CT images are obtained and then PET imaging [28]. The CT portion of the PET/CT may be performed with or without intravenous contrast; however, we do recommend using contrast, as it gives better anatomic delineation.

Diagnosis

PET has higher sensitivity in detection of pancreatic cancer (92%) than CT (87%) and MRI (69%); however, the specificity is much lower at

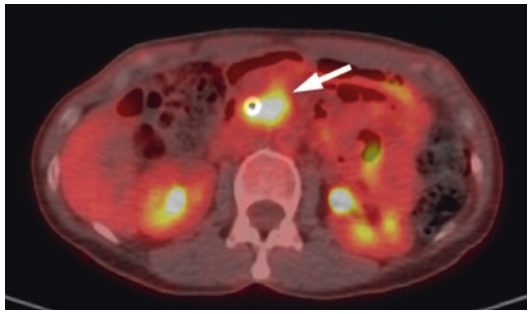

Fig. 5.9 Fused PET/CT image showing an avid mass in the head of the pancreas (arrow)

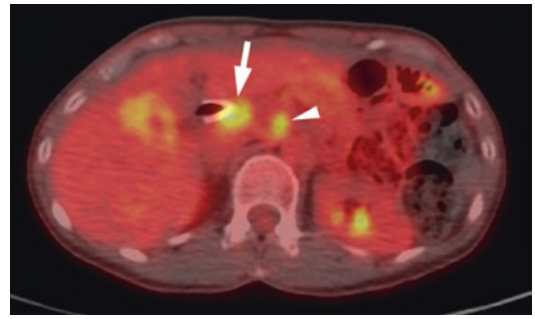

Fig. 5.10 Fused PET/CT image showing the presence of an FDG avid celiac lymph node (arrowhead) with an FDG avid pancreatic head mass (arrow)

65% compared to 96% and 93% for CT and MRI, given that the FDG uptake can be seen in other malignancies affecting the pancreas like metastasis and inflammatory processes like acute pancreatitis and mass-forming chronic pancreatitis (Fig. 5.9) [30]. These findings correlate with previously reported meta-analysis studies [31–34].

Staging

PET/CT is limited in local tumor (T) staging of the pancreatic cancer due to the common use of un-enhanced CT component as well as relatively poor spatial resolution when compared to multiphase enhanced CT. The extent of tumor involvement of peripancreatic vessels and organs cannot be well evaluated with PET/CT, thus, requiring more accurate evaluation with another modality including multiphasic CT, MRI, or EUS. If the patient is eligible for surgical treatment based on prior CT and/or diagnostic laparoscopy, it is preferred that the study is performed 1–2 weeks before scheduled surgery [35].

Nodal (N) disease is one of the most important prognostic factors affecting management in patients with pancreatic cancer. Accurate detection of metastatic lymph nodes is of extreme importance, since any positive lymph node outside of the surgical field is considered M1 and may preclude surgical resection (Fig. 5.10). On CT and MRI, the detection of metastatic lymph nodes is based on enlarged size (short axis size >1 cm); however, benign reactive lymph nodes

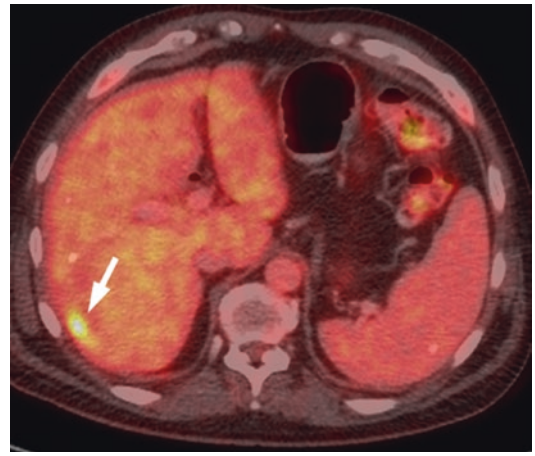

Fig. 5.11 Fused PET/CT image demonstrating an FDG avid liver metastasis (arrow) in a patient with pancreatic cancer

can also be enlarged, confounding the accurate staging. In particular, reactive lymphadenopathy can be seen after biopsy or biliary instrumentation. PET can also underestimate tumor involvement in small lymph nodes <0.5 cm due to its limited spatial resolution (5–8 mm). However, the odds of detection of these micrometastases are improved when there is significant elevation of CA 19–9 level and SUVmax of the primary tumor, especially when CA 19–9 values are above 240 U/mL and primary tumor SUVmax level is over 7.2 +/− 2.6 [36].

Distant metastatic (M) disease in PDAC is frequently detected in the liver, peritoneum, lungs, and bones (Fig. 5.11). PET/CT has shown to be superior in detecting bone metastasis. The

advantage of PET is the detection of distant metastasis. PET/CT was shown to be superior to PET alone in detection of hepatic metastasis (82% versus 67%, respectively). It is also superior to CT plus endoscopic ultrasound (EUS) in borderline resectable cases for detection of metastatic disease, sparing these patients from unnecessary surgeries. Several studies reported that PET resulted in staging changes in 27% and management changes in up to 11% of the patients [29, 33].

Treatment Response

PET is valuable in evaluation of treatment response or detection of progression of disease, since metabolic activity changes precede tumor size changes (Fig. 5.12). Prior prospective trials demonstrated that lower baseline and post-chemotherapy SUVmax on PET was predictive of histological response. Also, SUVmax, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) may be significant prognostic factors [37]. In the neoadjuvant setting, if there is progression of disease, patients can be spared from undergoing an unnecessary operation with a high morbidity and in the adjuvant setting, an adjustment or change of chemotherapy regimen can be performed based on changes in metabolic activity of the tumor on PET/CT.

Detection of Recurrent Disease

Contrast-enhanced CT is the most frequently used modality for detection of recurrent disease. But in certain cases, including patients who cannot undergo contrast-enhanced CT due to renal failure or contrast allergy or in patients with suspected recurrence due to mild or equivocal elevations of CA 19–9 without morphologic signs of disease recurrence; PET/CT has clear value, detecting metabolically active disease. PET/CT has sensitivity of 91%, specificity of 100%, and accuracy of 92% for detection of recurrent pancreatic cancer [38].

Magnetic Resonance Imaging

MRI Protocol

MRI for diagnosis and staging of pancreatic cancer may be performed on a 1.5 or 3.0 Tesla gradient systems using cardiac 16 channel coils phased-array torso coils to improve the signal-to-noise ratio. An MRI protocol should include a single-shot fast spin-echo (SSFSE) sequence in the coronal plane, an axial fat-saturated T2 FSE sequence, a T1 gradient echo (GRE) fat-saturated sequence, and a post-contrast 3D dynamic GRE sequences in arterial, portal, and delayed phases. Diffusion weighted imaging (DWI) has been

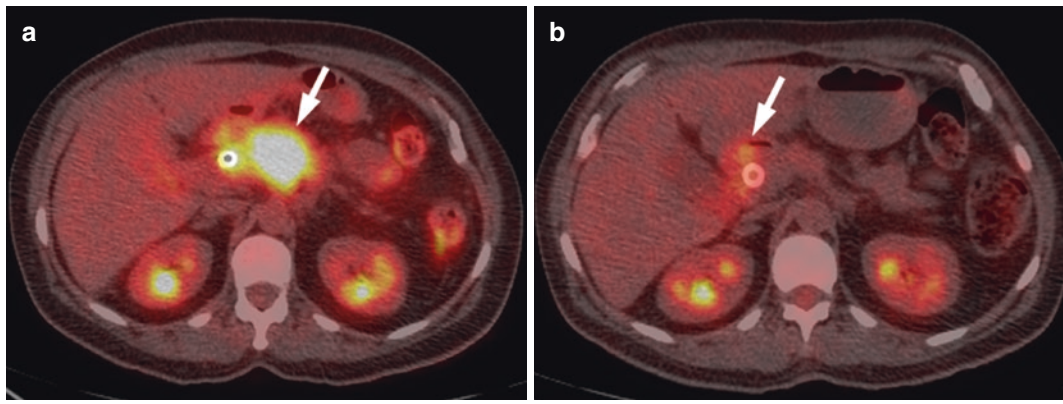

Fig. 5.12 Fused PET/CT images demonstrating (**a**) the pre-adjuvant therapy scan with FDG avid pancreatic head mass (arrow) and (**b**) decreased FDG avidity of the pancreatic head mass (arrow) suggestive of a favorable response to treatment in a patient with advanced pancreatic cancer

used in assessment of pancreatic cancers. Coronal and axial magnetic resonance cholangiopancreatography (MRCP) images are usually obtained. Fast imaging employing steady-state acquisition (FIESTA) or true fast imaging with steady-state free precession (Tru-FISP) images are performed to assess the vessels. The typical MRCP techniques involve fluid-sensitive sequences such as thin-section T2-weighted single-shot fast spin-echo (HASTE/SSFSE) and thick-slab T2-weighted half-Fourier SSFSE MRCP and 3D respiratory-triggered or navigator-triggered techniques.

Diagnosis

Currently, MR is used as a "problem-solving" tool in patients with an inconclusive CT diagnosis or in suspected masses without contour deformity of the pancreas. MR can also be used for pre-operative staging in patients who are allergic to iodinated contrast agents or have renal insufficiency.

MRI has an excellent soft tissue resolution and can detect signal intensity changes within the pancreas. The normal pancreas has a high signal intensity on T1-weighted fat-suppressed sequences due to acinar proteins which shorten the T1 values of the normal gland [39]. The normal pancreas enhances maximally during the arterial phase of contrast enhancement [40]. PDACs are low in signal on the precontrast and the post-contrast images compared to the pancreatic parenchyma due to presence of fibrous stroma [39, 41]. On delayed phase, more than 1 min delay in enhancement may result in invisibility of pancreatic cancer, since the contrast diffuses through the capillaries and tumor becomes similar in signal to that of the pancreatic parenchyma [39]. However, it should be noted that differentiating small PDAC from focal chronic pancreatitis might be very difficult or impossible [42]. Both focal chronic pancreatitis and PDAC can appear as focal hypointense masses with associated dilatation of common bile duct and main pancreatic duct (double-duct sign). Both conditions may also demonstrate ductal strictures, infiltration of the adjacent fat, arterial encasement, or venous obstruction [43]. There are often no distinguishing features on T1- and T2-weighted MR imaging [44]. Specific imaging features that favor an inflammatory mass are non-dilated or smoothly tapering pancreatic and bile ducts coursing through the mass ("duct-penetrating" sign) [45], irregularity of the pancreatic duct, and the presence of pancreatic calcifications. In contrast, a smoothly dilated pancreatic duct with an abrupt interruption prior to the ampulla favors the diagnosis of cancer (Fig. 5.13). Other feature that favors cancer is a mass at the site of obstruction resulting in distal

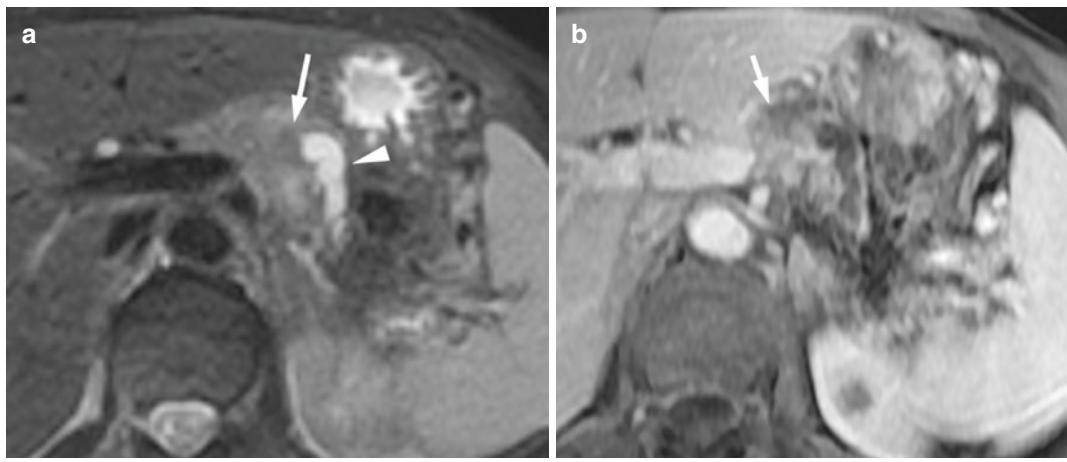

Fig. 5.13 (**a**) Axial T2 weighted MR image demonstrates dilated pancreatic duct (arrowhead) with abrupt cut off due to pancreatic cancer (arrow) and (**b**) corresponding post-contrast MR image demonstrates a hypoenhancing mass (arrow) at the location of ductal cut off consistent with pancreatic cancer

atrophy of the pancreas [46]. A mass causing upstream chronic pancreatitis can sometimes be detected on early phase dynamic gadolinium-enhanced images. The cancer sometimes is seen as a focal hypointense mass relative to the hypoenhancing region of chronic pancreatitis on early gadolinium-enhanced images [46]. The combined MRI features of a focal pancreatic mass, pancreatic duct dilatation, and parenchymal atrophy are highly suggestive of ductal adenocarcinoma [42].

Approximately less than 50% of patients with pancreatic adenocarcinomas exhibit mildly hyperintense signal intensity on T2-weighted images [47]. The T2 signal intensity of PDAC may depend on the amount of desmoplastic reaction within the tumor and the degree of intratumoral necrosis as necrotic tumor may have a high T2 signal intensity. On MRCP, a double-duct sign is the common indirect sign which suggests presence of a pancreatic neoplasm, where the pancreatic duct and the common bile duct are both obstructed by the tumor [48]. A study reported a specificity of 97% and a sensitivity of 84% for MRCP images in the detection of pancreatic adenocarcinoma based on these findings [49]. On DWI, the PDAC demonstrates diffusion restriction and has a high signal intensity relative to the surrounding pancreatic tissue. Apparent diffusion coefficient (ADC) is a calculated value from a DWI sequence. One study showed that ADC values were able to differentiate pancreatic cancer (1.44 ± 0.20), compared to that of normal pancreas (1.90 ± 0.06) and tumor-associated chronic pancreatitis (2.31 ± 0.18) [50]. The sensitivity and specificity of MRI including T1-weighted 3D-GRE sequences for differentiating pancreatic carcinoma from chronic pancreatitis were 93% (13/14) and 75% (6/8), respectively [51].

Staging

Currently, complete resection provides the only potential cure for pancreatic adenocarcinomas. Classic contraindications for resection include involvement of the celiac axis, SMA encasement and organ invasion other than the duodenal, and mesenteric infiltration. 3D Dynamic post-contrast T1 weighted imaging is a valuable tool to assess vascular encasement [47, 48] and can help in local staging of pancreatic cancer. The tumor in the pancreatic head can spread into the root of the mesentery, along the left jejunal vascular branches and the common hepatic artery resulting in unresectable tumor [52]. These findings can be well visualized on the post-contrast T1 weighted sequence or the FIESTA/tru-FISP sequences.

Liver is the most common site of distant metastasis in pancreatic cancer. Hepatic metastases from pancreatic cancers are low in signal intensity relative to the hepatic parenchyma on both fat-saturated and non-fat-saturated T1 weighted images. They are slightly hyperintense relative to the hepatic parenchyma on T2 weighted images during the short TE (time to echo) sequence and demonstrate irregular rim enhancement on the arterial phase. Signal intensity may be low in the center of the lesion because of the primary cancer's desmoplastic nature. Transient, ill-defined, peritumoral enhancement in the hepatic parenchyma may be present on the arterial phase of contrast enhancement. Perilesional enhancement is typically wedge-shaped and is usually present in small, hypervascular, and subcapsular liver metastases; these metastases are observed in more than 80% of the patients and may be the only site of metastases in up to 20% of the patients [53, 54]. Since the patients with pancreatic cancer frequently undergo biliary procedures and biopsies, they are prone to develop cholangitis and hepatic abscesses which can mimic metastasis. Asymptomatic focal cholangitis may present as a new hepatic lesion with restricted diffusion similar to metastasis. Hepatic abscesses tend to have T2 hyperintense signal with peripheral rim enhancement and would resolve following antibiotic therapy [55].

Assessment for metastatic lymph nodes may be difficult on MRI. On any cross-sectional imaging modality metastases to the lymph nodes are based on size. Lymph nodes >1 cm in the short axis are considered metastatic. However benign lymph nodes can also be enlarged leading to a

false negative diagnosis, similarly lymph nodes containing micrometastases may be of a normal size. Lymph nodes, which are centrally necrotic and have a high signal on the T2 weighted images, may be considered metastatic and this feature has a high specificity.

Assessment of Recurrent Cancer

Local recurrence post-surgery may appear as infiltrating soft tissue mass on the post-contrast T1 weighted sequence. The soft tissue thickening may be present along the vessels and the nerves specifically posterior to the SMA and SMV, at the surgical margin. Differentiating between tumor recurrence and post-inflammatory stranding may be difficult to diagnose in the early postoperative period. Recurrent tumor in the surgical bed can infiltrate into the adjacent stomach and the jejunal loops and along the hepatico-jejunostomy, causing biliary obstruction. The tumor markers will be elevated in the setting of recurrent disease whereas will be normal when the soft tissue thickening just represents fibrosis or granulation tissue [56].

Conclusion

Imaging plays a significant role in diagnosis, staging, and follow-up of pancreatic cancer. There are several entities including mass-forming focal pancreatitis, autoimmune pancreatitis, neuroendocrine tumor, or metastasis that can mimic pancreatic cancer. Each imaging modality has strengths and weaknesses for detection, staging, and follow-up of pancreatic cancer. CT is the main and most common imaging modality for evaluation and staging of pancreatic cancer. PET/CT can be used for detection and follow-up but is less frequently used for staging. MRI is mostly used for problem-solving and evaluation of hepatic lesions. Overall, pancreatic cancer should be evaluated with appropriate imaging in conjunction with tumor marker and clinical presentation of the patient. In some cases, multiple imaging modalities are needed for thorough evaluation of the patient.

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6 Diagnosis and Staging of Pancreatic Cancer: Laparoscopy

Eileen C. Donovan and Michael P. Kim

Introduction

Approximately 82% of patients with PDAC have regional lymph node invasion or metastasis at the time of diagnosis. Based on Surveillance, Epidemiology, and End Results (SEER) data, 53% of PDAC patients present with distant metastases, 29% have radiographic evidence of regional lymph node involvement/lymphadenopathy, and the remaining present with potentially resectable disease [1]. Following surgical resection with negative microscopic margins (R0 resection), the median overall survival for PDAC patients is reported to be only 23 months, highlighting the likely systemic nature of PDAC and the likely presence of occult metastases in the absence of gross metastatic disease [2]. Due to the high likelihood for macroscopic or microscopic metastatic disease being present at the time of diagnosis, it is imperative to accurately stage and manage PDAC patients with local and systemic therapies to maximize lifespan and quality of life.

Among patients who are deemed to have localized, resectable tumors, a portion is found to ultimately have unresectable disease due to occult metastatic lesions at the time of their planned resection, with reported rates ranging from 8 to 15% in recent literature [3, 4]. Many of these patients ultimately undergo nontherapeutic laparotomies despite improvements in accurate staging with pancreatic protocol CT scans, a triple-phase, thin-slice multidetector CT scan consisting of early arterial, pancreatic, and portal venous phases. Given the morbidity of laparotomy, the use of staging laparoscopy is a valuable adjunct to assist in the identification of occult metastatic disease prior to proceeding with definitive surgical resection. Beyond its utility as a procedure immediately preceding a planned laparotomy, laparoscopy also has important roles throughout the entire diagnostic and treatment algorithm of PDAC, such as assisting in upfront staging prior to neoadjuvant chemotherapy, restaging of new lesions during chemotherapy, post-resection surveillance, and obtaining tissue for translational research and clinical trials. Accordingly, in this chapter we highlight the various roles of diagnostic laparoscopy in PDAC patients with particular emphasis on its use in the preoperative and postoperative settings.

History

Although the routine use of laparoscopy in the workup and staging of PDAC varies by institution, it is not a new concept. Cuschieri described the use of laparoscopy in a series of 23 patients with cancer of the pancreas or periampullary

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_6

region from 1973 to 1977 [5]. On laparoscopic evaluation, 5/15 patients with obstructive jaundice and 6/8 patients without obstructive jaundice were found to have metastatic disease. Given that the use of CT imaging was not yet routine in the workup of suspected PDAC at this time, laparoscopy was primarily used for diagnosis rather than to identify occult metastasis. As imaging techniques improved, the role of laparoscopic surgery has shifted. In the mid-1980s, Warshaw and colleagues explored the use of laparoscopy for the detection of occult metastases in 40 patients with biopsy-proven PDAC deemed resectable on radiographic staging [6]. On laparoscopic evaluation, metastatic lesions were found in 14/40 patients. Of the remaining 26 patients, 3 more were found to have metastatic lesions upon conversion to laparotomy. Studies throughout the 1990s continued to demonstrate the utility of staging laparoscopy in the identification of undiagnosed metastatic disease prior to surgical resection [7, 8]. However, it is important to note that not all of these studies excluded patients with locally advanced tumors, a population at higher risk of having occult metastatic disease. Further, there was no universal definition of what constituted a resectable tumor based on preoperative imaging at this time [9].

Despite studies that documented the value of staging laparoscopy in the detection of occult disease, some critics argued the need for surgical bypass with hepaticojejunostomy or gastrojejunostomy validated upfront laparotomy without preceding laparoscopy. However, in a study of 155 patients found to have unresectable PDAC on laparoscopic staging, only 3 required subsequent laparotomy due to biliary and/or gastric outlet obstruction [10]. In particular, the utilization of metal endobiliary stents as a safe and effective alternative to hepaticojejunostomy has decreased the need for surgical intervention for malignant biliary obstructions [11, 12]. A recent retrospective study found that patients who underwent palliative biliary metal stent placement and gastrojejunostomy had significantly decreased biliary complications compared to those who underwent both hepaticojejunostomy and gastrojejunostomy (0% vs. 11%, $p = 0.037$) [13]. Further, the advancement in the fields of laparoscopic and robotic surgery has provided surgeons the ability to treat malignant gastric outlet obstruction through minimally invasive approaches. As the evidence against the need for laparotomy and prophylactic bypass in patients with metastatic disease has grown, laparoscopy has largely retained its role in staging of PDAC.

Review of Contemporary Data

Diagnostic Accuracy and Outcomes

The primary role of laparoscopy in PDAC is to identify intra-abdominal metastatic disease not observed on preoperative imaging prior to proceeding with a laparotomy. With current imaging technology, the sensitivity of CT imaging for liver metastases in pancreatic cancer is approximately 75% and even lower at 7% to 50% for peritoneal disease <1 cm [14]. Thus, despite improvements in imaging quality, the 8–15% of patients found to have occult metastatic disease at the time of their planned resection have persisted. A recent single-center retrospective study of 1001 patients with resectable PDAC based on preoperative imaging found that 151 patients (15%) had previously undiagnosed metastatic disease at the time of surgery [4]. Within this cohort, 89/151 patients (59%) underwent staging laparoscopy and 62/151 patients (41%) underwent laparotomy. In the 89 patients who were initially evaluated for occult metastatic disease laparoscopically, staging laparoscopy diagnosed metastatic disease in almost all patients, with only 1 patient diagnosed after conversion to laparotomy. Gemenetzis et al. found that 8.2% of patients who presented for surgical resection of PDAC had occult metastatic disease on exploration [3]. Of those patients, only 24% underwent a minimally invasive initial evaluation. Similarly, another series examining 77 patients with potentially resectable PDAC found that 7/25 patients examined with laparoscopy were found to have metastatic disease, compared to 5/52 patients who underwent laparotomy without preceding laparoscopy [15].

Though the aforementioned studies are limited by their single-center, retrospective nature, reported findings are supported by meta-analyses. For example, a 2016 international meta-analysis of 16 studies found that despite adequate CT staging, patients still had a 41.4% chance of having unresectable disease due to local invasion or metastasis at the time of surgery [16]. With the addition of diagnostic laparoscopy, this probability decreased to 20%. Given these results, the authors concluded that the use of diagnostic laparoscopy could avoid an unnecessary laparotomy in approximately 21% of patients who present for resection with curative intent. It is important to note that this review included pancreatic and periampullary cancers, and that there were no consistent criteria for qualifying resectable tumors across the study timeframe and between institutions.

As previously mentioned, laparotomy and surgical bypass with either hepaticojejunostomy or gastrojejunostomy was formerly the standard of care in patients with locally advanced or metastatic disease due to the concern for the development of biliary and gastric outlet obstruction. However, an early study by Espat et al. examining 155 patients with locally advanced or metastatic pancreatic adenocarcinoma on diagnostic laparoscopy found that only 3 required subsequent laparotomy due to biliary or gastric outlet obstruction [10]. Similarly, a more recent retrospective study found no significant difference in the lifetime incidence of gastric outlet obstruction in patients with occult metastatic disease who underwent laparoscopic evaluation versus laparotomy (7% vs. 6%, $p = 0.61$) [4]. With the reported low incidence of malignant obstruction and availability of minimally invasive techniques such as ERCP and biliary stenting, prophylactic bypass is no longer routinely indicated and should not preclude the use of laparoscopy.

When evaluating the utility of laparoscopy in the oncologic setting, the morbidity of a nontherapeutic laparotomy must also be taken into account. A recent study utilizing data from the National Surgical Quality Improvement Program (NSQIP) found that postoperative deep venous thromboses and surgical site infections occurred less frequently in patients who underwent diagnostic laparoscopy as opposed to nontherapeutic laparotomy, laparotomy with resection, or laparotomy with surgical bypass [17]. Further, there is emerging evidence that staging laparoscopy may also affect patient survival. Patients who undergo laparoscopy not only have shorter postoperative lengths of stay (0.8 days vs. 6.9 days, $p < 0.001$), but they are also able to start or resume chemotherapy more quickly [4]. Sell et al. found that the immediate resumption of chemotherapy likely translated into a significant survival benefit, with an improved median overall survival in patients undergoing laparoscopy versus laparotomy (11.4 months vs. 8.3 months, $p < 0.001$). Given the prevalence of occult metastatic disease in PDAC patients, proceeding with a staging laparoscopy prior to laparotomy is a reasonable approach to decrease the rates of nontherapeutic laparotomies and the time to initiation or resumption of chemotherapy.

Cost-Effectiveness

The cost of any routine addition to a management algorithm must be considered when evaluating the feasibility and utility of its implementation. Though a trip to the operating room is certainly on the higher end of resource utilization, a study in the USA examining patients with borderline resectable pancreatic cancer found no significant difference in overall treatment cost in those undergoing diagnostic laparoscopy prior to neoadjuvant chemotherapy compared to those that did not undergo laparoscopy [18]. A similar study in the UK in patients with presumed resectable pancreatic cancer found that diagnostic laparoscopy had a similar cost to direct laparotomy when laparotomy was scheduled for a subsequent admission [19]. Though differences exist between healthcare systems, variables such as admission length, unused operating room time, and number of anesthesia events can all have a significant impact on overall cost. Collectively, the evidence suggest that diagnostic laparoscopy is cost-effective, and cost should not preclude its use in appropriate patients. This claim is further sup-

ported by a decision tree model developed by Jayakrishnan and colleagues that shows that diagnostic laparoscopy prior to planned resection allows for cost reduction in both patients who receive neoadjuvant therapy and those who proceed directly to surgical resection [20]. Moreover, the costs and opportunity costs of diagnostic laparoscopy should be balanced with the relative costs and opportunity costs of nontherapeutic laparotomies and associated complications.

Principles of Management

Indications

Though the routine use of staging laparoscopy varies by institution, studies have examined risk factors for occult metastatic disease in an effort to identify which patients would most benefit from laparoscopic evaluation. Elevated preoperative CA 19-9 levels have been shown to be predictive of occult metastatic disease on surgical exploration, though the minimum cutoff value varies by study with ranges from >192 U/mL to >385 U/mL reported in the literature [3, 21–23]. Similarly, primary tumor size and tumor location in the body or tail of the pancreas have also been shown to be predictive of occult metastasis [21, 24]. For example, a single-center retrospective study found that CA 19-9 levels >192 U/mL and primary tumor size >30 mm were predictive of occult metastatic disease in patients presenting for curative resection on multivariate analysis [3]. Though no formal diagnostic algorithm exists, De Rosa and colleagues proposed that patients with resectable disease based on preoperative imaging undergo a diagnostic laparoscopy if CA 19-9 was ≥150 U/mL or tumor size was >3 cm [25]. Current guidelines from the National Comprehensive Cancer Network® (NCCN®) recommend considering the use of diagnostic staging laparoscopy in patients with borderline resectable disease or high-risk patients with resectable disease, such as those with a very high CA 19-9, large primary tumor, or large regional lymph nodes [26]. We generally perform staging laparoscopy for all patients with locally advanced or borderline disease, persistently elevated CA19-9 (particularly after neoadjuvant chemotherapy) in the absence of biliary occlusion, and in PDAC patients who have evidence of local or regional lymphadenopathy.

Table 6.1 Common indications for the use of staging laparoscopy in the diagnosis and treatment of pancreatic cancer

Common Indications for Staging Laparoscopy in Pancreatic Cancer
1. Upfront staging prior to neoadjuvant chemotherapy or surgery
2. Clarification of new lesions seen during neoadjuvant chemotherapy
3. Clarify liver lesions in a patient with underlying liver abnormality
4. Immediately preceding planned resection in patient with high risk lesion (ex: large tumor, high CA 19-9, large regional lymph nodes)
5. Surveillance and biospecimen acquisition during adjuvant therapy

Through a multitude of discussions at multidisciplinary tumor board and broad patient experience, we identify common clinical scenarios for which diagnostic laparoscopy is likely of highest yield (Table 6.1). We divide these into treatment phases—preoperative, intraoperative, and postoperative—for the purpose of algorithmic application and to illustrate potential changes in downstream management based on the findings of staging laparoscopy (Fig. 6.1).

Preoperative Setting

Staging Clarification Prior to Upfront Surgical Resection or Neoadjuvant Therapy

Diagnostic laparoscopy can be utilized as a complement to pancreatic protocol CT scans to assist in staging prior to upfront resection or neoadjuvant chemotherapy. Findings suspicious for metastatic disease on cross-sectional imaging may indicate staging laparoscopy if such findings are likely to be visualized, typically for peritoneal disease. Metastatic disease within solid organ parenchyma may undergo percutaneous biopsy if there is a high degree of clinical suspicion for metastatic disease. The identification of occult

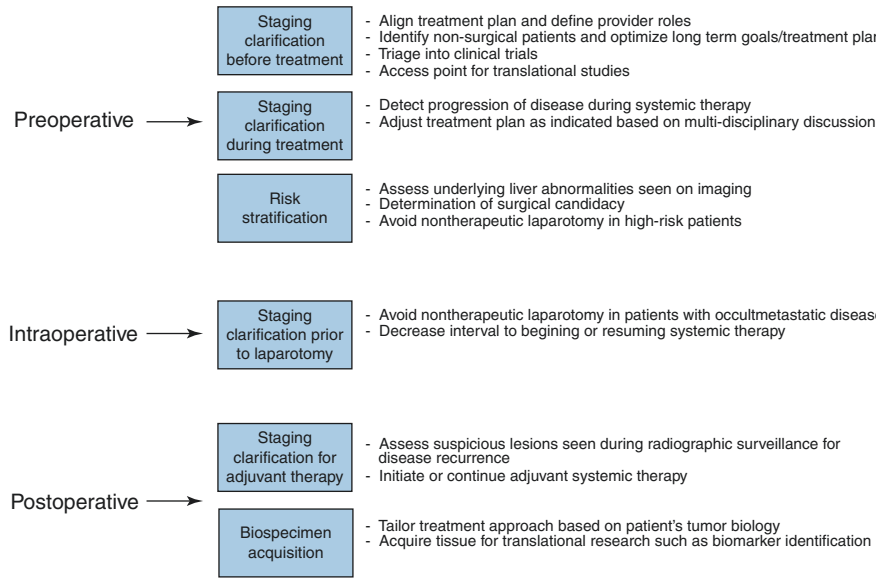

Fig. 6.1 Algorithms highlighting the points in which laparoscopy can be used in the diagnosis and surgical treatment of pancreatic cancer

metastatic disease at this point helps to define whether a patient is on a surgical pathway or non-surgical treatment pathway. Such resolution gives patients, caregivers, and their multidisciplinary team clarity on expected treatment plans and efficiently utilizes resources and determines necessary provider involvement.

Staging Clarification During Neoadjuvant Therapy

The appearance of new metastatic lesions in a patient undergoing chemotherapy indicates disease progression and often necessitates a multidisciplinary discussion regarding changes in the treatment plan. On occasion, laparoscopy can also be used to evaluate and biopsy new lesions seen on surveillance imaging during the course of neoadjuvant therapy. This can often be accomplished between cycles of chemotherapy without significant delays or interruptions to systemic therapy.

Risk Stratification Prior to Surgery

Occasionally, patients will present with radiographic findings concerning for comorbid conditions and associated focal abnormalities. For example, patients may present with liver abscesses, abnormal liver contour/scalloping, or possible nodular liver disease, all of which may affect downstream management decisions regarding staging or surgical candidacy. Diagnostic laparoscopy in such patients can be used to more accurately evaluate and confirm liver pathology and avoid nontherapeutic laparotomies in high-risk patient populations.

Potential changes in management based on preoperative staging laparoscopy:

1. Solidification of treatment pathway**:** Patients with metastatic disease should be treated with the appropriate systemic chemotherapy, and radiotherapy can be used as an alternative local therapy. Definitive radiation may be offered instead of treatment-specific administration of radiotherapy. The role of the surgeon may be minimized but not excluded. The goals and expectations of patients and providers are firmly clarified along with the anticipated clinical course and associated treatment plans.
2. Focus on long term treatment goals**:** Patients with metastatic disease should be treated with chemotherapy as the mainstay of therapy. As such, potential complications encountered during and between cycles of chemother-

apy—specifically biliary and duodenal occlusion—may be anticipated and should be addressed with durable treatment solutions.
3. Participation in clinical trials: As clinical trial eligibility is often determined by pretreatment status and clinical stage, patients may be efficiently enrolled in clinical trials specific to their stage. Discovery of metastatic disease prior to surgery may permit rapid enrollment in clinical trials in conjunction with standard of care chemotherapeutic regimens.
4. Access to biospecimen for translational studies: Acquisition of tumor tissue for translational studies is extremely limited with conventional FHA or core biopsies used for PDAC diagnosis. Since metastatic disease encountered during staging laparoscopy should be biopsied for formal, pathologic diagnosis, sizable tumor tissue may be harvested on IRB-approved research protocols for discovery and/or somatic sequencing to identify potential therapeutic vulnerabilities present in metastatic PDAC tumors. Such tumor-directed therapies, while not yet widely prevalent in PDAC, may nonetheless inform the subsequent selection of therapeutic agents.

Intraoperative Setting

Staging Clarification Immediately before Laparotomy

Following the completion of neoadjuvant chemotherapy, staging laparoscopy can be performed immediately preceding planned surgical resection in high-risk patients, such as those with a large primary tumor, persistently elevated CA 19-9, or enlarged regional lymph nodes. Benefits of staging laparoscopy compared to laparotomy include decreased length of stay (0.8 days vs. 6.9 days, $p < 0.001$) and decreased rate of wound infections (2% vs. 11%, $p = 0.03$). Most importantly, avoiding a nontherapeutic laparotomy allows a patient to more quickly start or resume systemic chemotherapy, which has been shown to translate to a survival benefit [4].

Potential changes in management based on intraoperative staging laparoscopy:

1. Avoidance of nontherapeutic laparotomy: Patients may be spared all elements of a nontherapeutic laparotomy and associated morbidity. Patients may often be discharged from the hospital the same day as planned surgical resection and saved the financial and logistic costs of a prolonged inpatient hospital stay. Management teams may efficiently align on subsequent treatment plans.
2. Short interval to system therapy: Patients can be spared prolonged disruptions in systemic chemotherapy and may begin or resume such treatment only days to weeks after laparoscopy. Wound complications associated with systemic chemotherapy are minimized compared to large incisions made during nontherapeutic lapaorotomies. Moreover, robust PDAC patients who would otherwise qualify for pancreatic resection may be rapidly enrolled in clinical trials on a selective basis.

Postoperative Setting

Staging Clarification for Adjuvant Therapy

Patients undergoing postoperative adjuvant therapy require continued surveillance for disease recurrence. If new lesions are seen on surveillance imaging, particularly if the abnormality involves the liver surface or peritoneum, laparoscopy can occasionally be used to visually evaluate and obtain biopsies to confirm or rule out recurrent disease. Of note, most of the time disease recurrence is best determined by imaging; however, if imaging characteristics are unclear or inconsistent with recurrent PDAC, laparoscopy can be used for clarification. If metastatic recurrence is confirmed, patients should be treated with systemic therapy as indicated based on the time of recurrence and their initial primary therapy.

Biospecimen Acquisition

Laparoscopy provides a minimally invasive method of obtaining tissue specimens that can be utilized for translational research such as the development of future therapies for PDAC and

identification of tumor biomarkers. For the individual patient, tumor specimens can be sequenced or developed into patient-derived organoids that can potentially inform treatment decisions.

Potential changes in management based on postoperative staging laparoscopy:

1. Administration of adjuvant systemic therapy: The mainstay of treatment for recurrent PDAC is systemic therapy. If recurrent PDAC is confirmed on diagnostic laparoscopy, treatment teams may elect to treat the patient with adjuvant therapies to potentially extend lifespan. This is particularly important for patients not currently on therapy as official confirmation of recurrent PDAC may serve as a trigger for the initiation or continuation of chemotherapy.
2. Access to biospecimen for translational studies: Patients with stage IV PDAC have very limited lifespans and few, effective therapeutic options. Metastatic tumor acquired at the time of diagnostic laparoscopy, simlar to immediately prior to surgical resection, may be leveraged for translational studies, sequencing, and possibly subsequent treatment tailored to a patient's tumor. As technology and knowledge about PDAC biology grow, acquisition of biospecimen before and after surgical intervention will likely drive the selection of treatment options available to PDAC patients.

Technical Points

Staging laparoscopy can be performed immediately preceding laparotomy or scheduled as a separate surgery with formal oncologic resection to follow at a later date if no occult metastatic disease is found. Patients should undergo standard preoperative workup with appropriate risk assessment and optimization based on existing medical comorbidities. Absolute contraindications include the inability to tolerate anesthesia or pneumoperitoneum. It is important to identify patients with a history of prior abdominal surgery who have a high risk of intra-abdominal adhesions and those with underlying liver disease who may have abdominal wall varices, both of which can affect port placement.

Patients should be placed in the supine position on the operating room table with the arms appropriately padded and either tucked or extended on arm boards. If the staging laparoscopy is performed immediately preceding a planned formal oncologic resection, the patient should be prepped and draped in anticipation of a laparotomy. A standard staging laparoscopy is outlined below and illustrated in Fig. 6.2.

1. Placement of a 30° laparoscope through a 10 mm periumbilical port.
2. Examination of the peritoneal cavity for occult metastatic disease, paying particular attention to the surface of the liver and peritoneum.
3. Placement of additional 5 mm ports if needed to assist in exposure and visualization.
4. Biopsy and frozen sectioning of any suspicious nodules.

Though routinely used in the staging of other malignancies, the use of peritoneal washing remains controversial in PDAC. A single-center retrospective study found that in patients who underwent resection for PDAC, positive peritoneal cytology was associated with worse overall survival (8 months vs. 16 months, $p < 0.001$) [27]. According to current staging guidelines, positive cytology from peritoneal washings is considered M1 disease. If metastatic disease is found during laparoscopy, the patient is no longer a candidate for resection, and the operation is aborted.

Drawbacks

Despite that staging laparoscopy is a relatively low risk operation, concerns have been raised about its use in pancreatic cancer, such as the possible effect of laparoscopy on intra-abdominal tumor cell dissemination and trocar-site seeding. A single-center retrospective review of 235 patients with pancreatic cancer found no signifi-

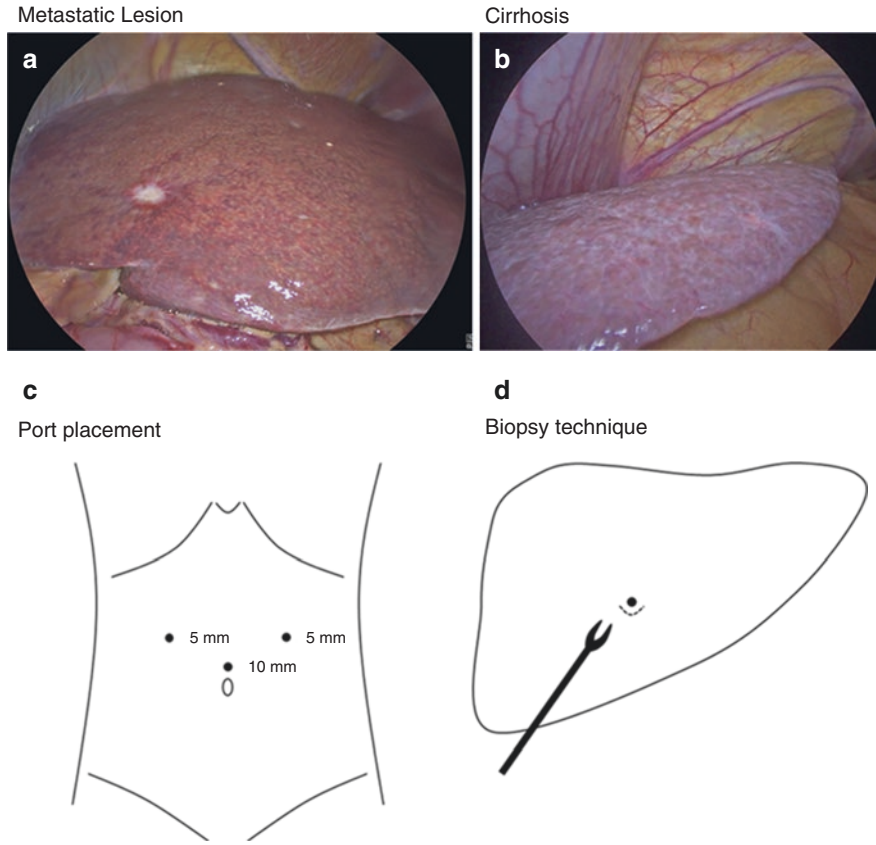

Fig. 6.2 Representative images demonstrating potential findings during diagnostic laparoscopy which include (**a**) a metastatic lesion on the surface of the liver and (**b**) cirrhosis. Port placement is shown in (**c**). Proper biopsy technique of liver lesions is demonstrated in (**d**), which includes utilizing electrocautery in a curvilinear fashion (dotted line) on the surface of the liver prior to sharply excising the lesion with laparoscopic scissors

cant difference between trocar-site recurrences in laparoscopy (3%) versus incision-site recurrence in laparotomy (3.9%) [28]. Overall, staging laparoscopy is a safe operation in the setting of pancreatic cancer with minimal risk beyond the standard risks of laparoscopic surgery.

Conclusion

In summary, staging laparoscopy is a safe, accurate, and cost-effective strategy to assist in the identification of radiographically occult metastatic disease prior to proceeding with laparotomy in patients presenting for resection of pancreatic adenocarcinoma. It can be performed immediately preceding a planned laparotomy or as a separate operation. Though its routine use varies by institution, patients who may particularly benefit from this approach include those with high preoperative CA 19-9 levels, large primary tumors, large regional lymph nodes, and pancreatic body/tail lesions. By avoiding the morbidity of a nontherapeutic laparotomy, patients are able to recover more quickly and resume or begin further treatment as indicated.

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7 Diagnosis and Staging of Pancreatic Cancer: Role of Gastroenterologist: Endoscopic Ultrasound (EUS), EUS-Guided Biopsy

Brian R. Weston and Emmanuel S. Coronel

Introduction

Endoscopic ultrasound (EUS) has dramatically evolved since its development in the early 1990s enabling the gastroenterologist to play a major role in the detection, diagnosis, staging, and management of pancreatic cancer [1, 2]. The availability of EUS technology and dedicated EUS training programs continues to expand across many regions of the world. In the USA, analysis of a 5-year trend from 2006 to 2010 using a Medicare database demonstrated the use of EUS-FNA for tissue acquisition in pancreatic diseases increased by 69.3% [3]. In 2018, the value of the North American EUS market was $296.9 Million USD. The global EUS market size was $830.6 Million USD in 2018 and is projected to reach $1375.6 Million USD by 2026 [4]. We will summarize the current role of EUS in pancreatic cancer in the following chapter.

Detection and Diagnosis

EUS allows for high-resolution sonographic imaging of the pancreas from the stomach and proximal duodenum which has proven especially advantageous for detection of small cancers (e.g. ≤2 cm) [5–7]. Multiple comparative studies have demonstrated EUS to be superior to CT [5, 8–12]. EUS also facilitates tissue acquisition of the pancreas that was previously only possible by more invasive percutaneous or surgical techniques [8], Fig. 7.1. Since the first reported case of EUS performed to sample a pancreatic lesion in 1992 by Vilmann et al., we have seen many significant advances to enhance the efficacy and safety of the procedure [13].

EUS-guided fine needle aspiration (FNA) and/or biopsy (FNB) has become the procedure of choice to obtain tissue to make a cytologic or histologic diagnosis of pancreas cancer. The differential diagnosis for a solid pancreatic mass includes both malignant and benign causes.

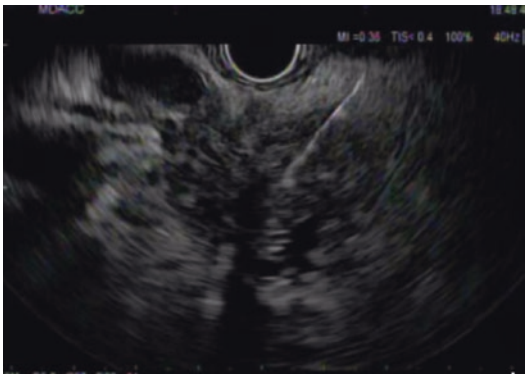

Fig. 7.1 Endosonographic image fine needle aspiration of an obstructing pancreatic head mass

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_7

Adenocarcinoma is by far the most common malignant cause accounting for at least 85% of solid pancreatic masses, Table 7.1; however, other causes include lymphoma, acinar cell carcinoma, neuroendocrine tumors, solid pseudopapillary tumors, and metastatic disease such as from renal cell carcinoma, malignant melanoma, breast, lung and colorectal cancer. Benign conditions such as autoimmune pancreatitis, focal pancreatitis, and some cystic lesions (microcystic serous cystadenoma) can also mimic malignant solid tumors on imaging. Therefore, establishing a correct diagnosis is essential to guide appropriate management. Only about 20% of patients with pancreas adenocarcinoma present with potentially resectable tumors [14]. The increasing use of neoadjuvant chemotherapy in patients with potentially resectable pancreatic adenocarcinoma also mandates pretreatment tissue confirmation. Nonetheless, the decision to obtain a tissue diagnosis still varies across medical practices and is often based on multiple patient factors.

The efficacy of EUS-FNA for a cytological diagnosis of solid pancreatic masses has proven to be very accurate with a high pooled sensitivity of ~85–89%, specificity ~96–99%, positive predictive value ~98–99%, and negative predictive value ~65–72% according to multiple meta-analyses. EUS-FNA is especially useful for lesions that are equivocal by imaging and lesions smaller than 2 cm compared to percutaneous sampling [8–10, 15–21].

An indeterminate diagnosis (i.e. report of atypia or only suspicion for malignancy) or false negative may still occur in ~15-20% of cases for any number of reasons [9, 20, 22–27]. Dedicated pancreatic protocol cross-sectional imaging should be performed prior to EUS not only for localization of the pancreatic tumor but also to evaluate for metastatic disease. Surrounding anatomy such as atrophic parenchymal changes, abrupt cutoff of a dilated main pancreatic or common bile duct or invasion of locoregional vascular structures may tip off the presence of an occult mass. When a high degree of suspicion for malignancy exists, non-diagnostic results necessitate careful re-evaluation of cytopathologic slides and communication with your pathologist. Repeat sampling versus close observation and in rare instances surgery may be appropriate. Repeat EUS-FNA is recommended as the second line test when there is a strong clinical suspicion of malignancy [9, 20, 28–32]. False positive results may occur in up to 5% [9, 33, 34].

Many factors may affect the quality and quantity of a specimen potentially influencing the diagnostic yield of EUS-guided sampling of pancreatic lesions, Table 7.2. Techniques to optimize yield have been the subject of much study and

Table 7.1 Differential diagnosis of malignant and solid pancreatic lesions [27]

Malignant tumors
Primary pancreatic ductal adenocarcinoma
Neuroendocrine tumors
Solid pseudopapillary neoplasm
Lymphoma
Pancreatic acinar cell carcinoma
Secondary metastatic lesions to the pancreas For example, lung, breast, renal, prostate, melanoma, gastrointestinal tract carcinoma (esophageal, gastric, ampullary, colorectal), sarcoma
Malignant cystic lesion with solid components (mucinous cystadenoma or intraductal papillary mucinous neoplasm)
Benign tumors and pseudotumors
Focal pancreatitis and chronic pancreatitis
Autoimmune pancreatitis
Microcystic serous cystadenoma
Other masquerading lesions, i.e., splenule

Table 7.2 Potential factors affecting diagnostic yield during EUS-FNA for pancreatic lesions

Lesion location
Lesion size
Lesion nature
Lesion visualization
Rapid on-site cytologic evaluation (ROSE) availability
Needle size
Needle type
Number of passes
Stylet use
Suction technique
Sampling technique
Sample preparation
Endoscope position
Experience of endosonographer and cytologist

continue to evolve. Adjustment in technique and/or additional passes may be required to maximize diagnostic adequacy [27, 35, 36].

The nature of any given pancreatic lesion may have a significant impact on detection and diagnosis, including the presence of excessive fibrosis, necrosis, or reactive/inflammatory change. Well-differentiated pancreatic adenocarcinoma compared to moderately or poorly differentiated tumors may require a higher number of passes [37, 38]. Vascular tumors may decrease the diagnostic yield due to increased blood and clot. Larger tumors are more likely to be necrotic and fibrotic. The presence of underlying chronic pancreatitis can make diagnosis of malignancy challenging. The sensitivity of EUS-FNA is significantly lower in the setting of chronic pancreatitis [9, 39–41]. Potentially useful techniques in this setting include EUS-elastography and contrast-enhanced harmonic EUS which may facilitate distinguishing cancer from benign lesions and finding the optimal site where FNA can be performed with improved diagnostic yield. EUS elastography is a technique that allows real-time quantification of the hardness of lesion [42, 43]. By calculating the elasticity of tissue, it is possible to distinguish benign (soft) tissue from malignant (hard) tissue [7, 44–49]. Pancreatic adenocarcinoma typically has a hard or stiff appearance in comparison with pancreatitis, which is usually mixed. Contrast-enhanced harmonic EUS (CEH-EUS) enables real-time assessment of tissue vascularity which may also enhance diagnosis. The technique involves intravenous injection of an ultrasound contrast agent that can provide assessment of the microvascularization and perfusion patterns within a pancreatic mass which may enable recognition of better puncture sites based on differences in blood flow patterns. Pancreatic adenocarcinoma has a distinct hypovascular appearance compared with other processes such as neuroendocrine tumors or chronic pancreatitis and autoimmune pancreatitis, which have a hyper- or isovascular appearance [50–53]. CEH-EUS has yielded a sensitivity and specificity of 88 and 93% in a recent multicenter prospective trial, as well as benefits which have been observed by several other investigators [50, 54–58]. EUS elastography has demonstrated pooled sensitivities and specificities of 95–99% and 67–76% according to multiple meta-analyses [9, 45, 46, 59, 60]. The use of needle-based imaging devices such as confocal laser endomicroscopy is a method that allows real-time optical biopsy via passage of a miniprobe through the needle during EUS FNA but has been applied mostly to pancreatic cysts [61]. None of the aforementioned techniques has been widely adopted and it is unlikley they will completely replace the need for FNA.

The presence of rapid on-site cytologic evaluation (ROSE) of direct smears provides immediate intraprocedural feedback. Numerous studies have confirmed the benefits of ROSE in terms of increasing diagnostic yield of EUS FNA specimens by 10–30% [8, 30, 35, 38, 62, 63]. The diagnostic yield of cytology obtained by EUS-FNA with ROSE in most studies exceeds 90% [35]. In a recent meta-analysis, ROSE was associated with a 3.5% improvement in adequacy rates for EUS-FNA of solid pancreatic lesions [64]. ROSE may decrease the number of needle passes or suggest modification of techniques such as altering suction or changing needle size. More importantly, ROSE may avoid potential delays in treatment associated with the need for repeat procedures. Despite the benefits of ROSE, many centers are unable to offer this service, due to limited resources and/or cost restraints, despite some evidence that ROSE can be cost effective especially by avoiding repeating procedures. Reliability on gross visual assessment for tissue specimen adequacy by either the endosonographer or cytotechnician has been shown to be inferior to assessment by a cytopathologist; however, if no cytopathologist is available, assessment should be attempted [27, 65–67]. Direct communication with a cytopathologist is strongly encouraged to facilitate the interpretation of findings.

Optimal needle size has been the subject of much study. Available needle sizes at present include 25G, 22G, 20G, 19G. No needle size has demonstrated superiority over another in terms of diagnostic yield, accuracy, number of passes, or complication rate. The 25G and 22G needles are

most commonly used for cytologic sampling of the pancreas. However, the smaller 25G needle may have a slightly greater sensitivity and adequacy than 22G needles and is often preferred due to its flexibility and ease of puncture for pancreatic head lesions in which scope angulation is accentuated. Smaller needles may provide more cellular, less bloody specimens than larger needles especially for ROSE. Sensitivity, specificity, negative and positive predictive values, yield, and safety are comparable to 22G and 25G FNA needles [30, 35, 68, 69]. Needle selection for those who have a choice is a complex process and will ultimately depend on intraprocedural assessment of the lesion nature, location, and presence of ROSE.

A variety of needle types are now commercially available for EUS-FNA and EUS-FNB. Although FNA for cytology is usually adequate to diagnose most adenocarcinomas, it may not provide sufficient material in some cases. Some well-differentiated carcinomas as well as neuroendocrine tumors, lymphoma, autoimmune pancreatitis, or metastatic pancreatic lesions may require larger amounts of tissue for ancillary testing and/or better preservation of tissue architecture for diagnosis [8, 30, 70–72]. Many studies have focused on the use of the EUS core biopsy needles to enhance diagnostic adequacy. Cell block and/or histologic preparations (i.e. cell blocks and/or formalin-fixed and paraffin-embedded tissue fragments) should be considered especially when FNA fails with 22G or 25G with ROSE and when ROSE is not available or ancillary testing needed [35]. When ROSE is not available, combining EUS FNA cytology and histology significantly increases the sensitivity for malignancy diagnosis compared with either alone (89.9% vs. 68.1% for cytology p = 0.007 and 60% for histology (P.0.001) [73]. Experience with initial core biopsy needles including the 19G "Tru-cut" needle with automatic spring-loaded biopsy handle (e.g., Quick Core, Cook Medical) and subsequent 19G stainless steel needles was limited by high rates of failure and complications due to poor flexibility [71, 72]. These have been replaced with a variety of new needle types in recent years [35, 74]. More flexible (Nitinol or Cobalt-Chromium based) needles in a variety of sizes and cutting tips have been introduced including: forward bevel needles (Expect™; Boston Scientific); reverse bevel needles with side-slots (core-trap) (Pro-Core™; Cook Medical), fork-tip needles (SharkCore™; Medtronic), Franseen-tip needles (Acquire™; Boston Scientific), tri-tip needles (Trident™; Micro-Tech) [35], (Fig. 7.2). Randomized trials comparing FNA and FNB needles thus far have demonstrated that diagnostic efficacy, technical performance, and safety profiles of FNA and FNB needles are comparable [70, 75–79]. At present most studies show no significant benefit in using a core biopsy needle over FNA for determining the etiology of pancreatic masses but should be considered if EUS FNA is non-diagnostic, ROSE is unavailable, or a histologic diagnosis is required [35]. Combining FNA and FNB techniques may improve diagnostic yield in some cases especially when ROSE is not available. The use of large needles does have disadvantages including increased tissue crush artifact, bloodier specimens, and increased difficulty acquiring specimen. Further studies are needed to determine the utilization and performance of different FNB needles.

The optimal number of passes to perform on any given solid lesion will depend on many factors. When ROSE is available, a diagnosis of adenocarcinoma is typically confirmed in under four passes. In our experience, a diagnosis of adenocarcinoma was achieved in 80% of the time with one pass and 90% in two passes [70]. If a diagnosis cannot be obtained after ~7–8 passes from the same site, then additional passes are unlikely to be diagnostic and might increase the risk of complications [35, 38, 80, 81]. When ROSE is unavailable, recommendations are for at least three to four needle passes with an FNA needle or two or three passes with an FNB needle [35]. A core biopsy needle does not appear to have an advantage over 22G or 25G FNA needles except for a reduced number of passes needed to obtain an adequate sample. No definitive endosonographic finding can predict the optimal number of passes for diagnostic yield [70].

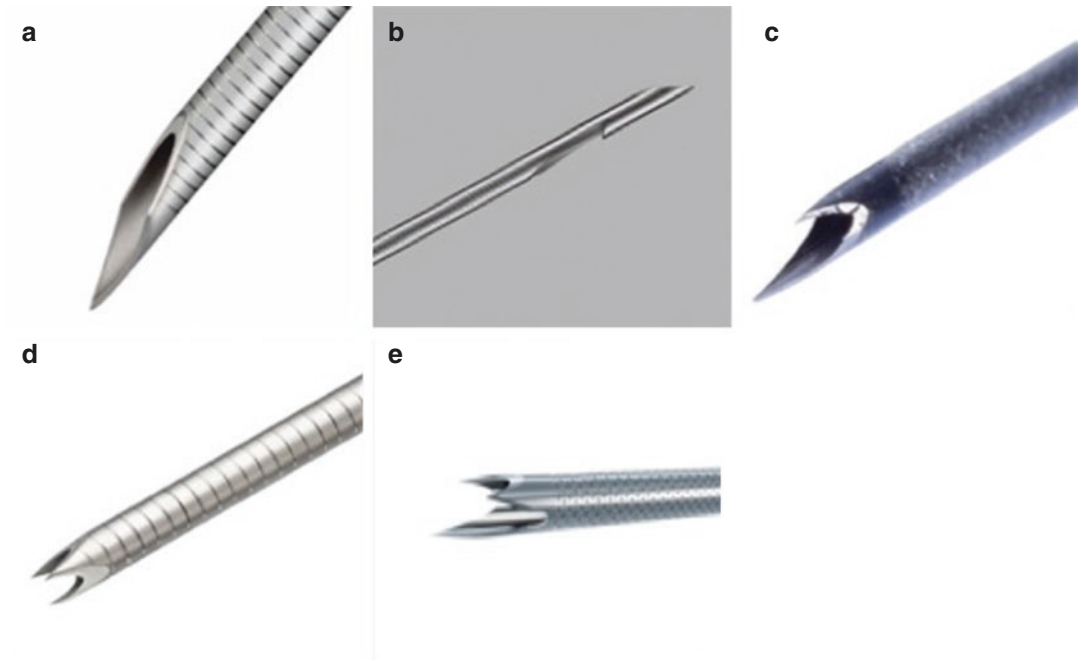

Fig. 7.2 Images of various needle designs available for fine needle biopsy (FNB): (**a**) Forward bevel type needle (Boston Scientific, Expect Flex™); (**b**) Menghini type needle with reverse side slot (core-trap) (Cook Medical, Echotip Pro-Core HD™); (**c**) "Fork-tip" type needle with multiple cutting-edge surfaces, opposing bevel design (Medtronic, SharkCore™); (**d**) Franseen type needle (Boston Scientific, Acquire™); (**e**) Tri-tip core needle (Micro-Tech Endoscopy, Trident™). [images used with permission courtesy of above]

A variety of sampling techniques have been described which may be adjusted based on the nature of the lesion. Standard technique typically involves multiple [5–10] to and fro "fanning" movements of the needle within the lesion to obtain a representative sample, although intervening vessels and scope position often dictate approach. For large lesions that may be centrally necrotic, targeting the periphery is recommended although this runs the risk of sampling reactive desmoplasia and inflammatory debris. Adjunctive techniques, such as contrast harmonic EUS-guided sampling and elastography discussed previously may be of benefit for targeting the optimal location in some instances. No single method is superior.

Several suction techniques have been described including standard suction (10–20 mL), high negative pressure (50 mL), slow stylet pull or capillary suction, and wet suction. Suction is intended to improve diagnostic yield by holding tissue against the cutting edge of the needle as it is moved within the lesion. However, suction has not consistently shown to improve diagnostic yield and may increase bloodiness or distortion of the tissue sample. Most endosonographers will adjust the strength of suction accordingly depending on nature of the aspirate. The role of suction varies depending on lesion and there is no consensus on its use [27, 30, 35, 74].

A stylet is commonly used during EUS-FNA to prevent occlusion of the needle lumen by intervening gastrointestinal tract tissue contaminant during puncture of the target lesion. Nonetheless, several randomized trials have noted that stylet use increases the bloodiness of the specimen and does not increase the diagnostic yield [30, 35, 82–86]. Current guidelines do not recommend for or against using the needle stylet for EUS-FNA sampling of solid masses and suggest using the needle stylet for EUS-guided sampling with FNB needles [35].

A variety of tissue sample preparation methods are currently utilized. Cytologic sample

processing typically requires preparation of smears. Interpretation of smears may be hindered by artifacts from cell degeneration, obscuring material, and drying effect even if the quantity of material is sufficient [87]. The method by which material is expressed from the needle onto a slide can influence diagnostic yield. Expulsion methods include reinsertion of the stylet and air-flushing with some studies showing preference for the ladder. The stylet allows for more control and removal of possible clot although it is more time consuming and possibly associated with an increased risk of needle injury [27, 85]. Air insertion may result in uncontrolled splatter of aspirate and air-drying artifacts or clotting of the specimen. Air-dried slides with Romanofsky (i.e. Diff-Quik) or Giemsa staining provide morphologic assessment for ROSE for preliminary diagnosis. Ethanol-fixed and Papanicolaou-stained material provides the best nuclear detail. Material may also be placed in liquid medium or fixative for cell block which can then be formalin-fixed, paraffin-embedded, and sectioned for standard hematoxylin and eosin staining or other ancillary testing. Cellblocks may be used as an adjunct but not a substitute for smears. Liquid based cytology preparations are also available. Microbiopsies for specimens ≥2 mm may be considered for conventional histology. Adequate preparation of FNA and FNB samples and dedicated training of cytopathologists is important for optimal results. At the current time, processing of EUS-acquired tissue specimens obtained has not been standardized and varies considerably between centers [35, 87, 88].

Multiple studies have demonstrated EUS FNA to have a steep learning curve with results that are operator dependent. Experience of the endosonographer is important with inherent variability in inter-operator performance [27, 88, 89].

The safety of EUS-FNA has also been well demonstrated (Ref. 25 in 2). Total complication rate for EUS-FNA in published series ranges from 0 to 13% and may be less than percutaneous sampling [2, 30, 89–91]. Acute pancreatitis is the most common complication but is still relatively infrequent in clinical practice with most studies reporting <1% risk. Other potential adverse events include infection, bleeding, perforation, tumor seeding, pain, and those related to sedation/anesthesia. A multicenter study in the USA demonstrated a complication rate of 0.28%, while a recent prospective study noted the complication rate of 0.85% [90, 92]. No definite association was found between the occurrence of a complication and the type and size of the pancreatic lesion, number of passes, or history of chronic pancreatitis [30]. The incidence of tumor seeding has been limited to case reports and has been demonstrated to be less than percutaneous sampling [91, 93–96]. Although the actual incidence of documented seeding may be underestimated, it is not believed to be clinically significant based predominantly on short overall survival of this disease and the fact that many patients receive systemic chemotherapy. Tumor seeding is of no consequence for surgical candidates who undergo transduodenal sampling of pancreatic head lesions as the duodenum is resected during Whipple surgery. Although transgastric FNA of resectable tumors located in the pancreatic body and tail is often avoided to prevent gastric wall seeding, a recent study showed preoperative EUS-FNA is not associated with adverse perioperative or long-term outcomes in patients undergoing distal pancreatectomy for solid neoplasms of the pancreas [8, 97, 98].

Staging

In addition, EUS may also be useful for advanced staging including sampling of locoregional or distant lymph nodes, tumor vascular involvement, accessible livers lesion, and the presence of small ascites undetected by other imaging. EUS may detect unsuspected metastasis in up to 10% of patients [99–102]. The pooled sensitivity and specificity of EUS for the detection of tumor vascular invasion range from 66 to 86% and 89 to 94%, respectively [7, 103–105]. The sensitivity of EUS varies according to the target vessel. For instance, the sensitivity of EUS for tumor invasion of the portal vein is over 80% in comparison with CT. By contrast, the sensitivity of EUS is low for the SMV, SMA, and celiac artery [7,

106]. EUS-FNA of remote malignant intravascular thrombi (noncontiguous to the primary tumor) has also been described which can significantly impact staging [107].

Management

The role of the EUS has been expanded to involve many aspects of pancreas cancer management as demonstrated in Table 7.3 and discussed in other chapters. Some are currently used in clinical practice and some are investigational.

Adjuvant Molecular Testing

A variety of molecular techniques have been recently investigated to better characterize the biology of pancreatic tumors from EUS obtained tissue specimens. Molecular profiling using several biomarkers such as K-ras, p53 tumor protein, CDKN2A/P16, SMAD4, microRNAs, hENT1 has been studied to enhance diagnosis (in cases when cytology is indeterminate), staging, prognosis, and treatments response for more personalized cancer care [2, 87, 108–117]. Organoid creation of EUS-acquired tissue is an exciting development for translational research and personalized treatment of pancreatic cancer. Organoids may be used for basic research tumor biology and to guide patient specific chemotherapeutic drug sensitivity testing. Next generation sequencing of tumor tissue allows panel testing for specific groups of mutations that are associated with PDAC [118, 119]. For molecular characterization both the quality and the quantity are important. Approximately 5–10 ng of DNA is necessary to detect mutations using next generation sequencing [119–121].

EUS-guided portal vein sampling has also been recently investigated for detection and enumeration of circulating tumor cells (CTCs). Early studies have demonstrated higher concentrations of CTCs in portal vein versus peripheral blood. The identification of high concentration of CTCs in portal vein blood may be used for possible sequencing and organoid creation or the so-called liquid biopsy [122–124].

Table 7.3 Applications of EUS for the management of pancreas cancer and its complications

EUS screening and surveillance for patients at high risk for pancreatic cancer, i.e. significant family history or genetic risk factors, cysts [6, 125, 126]
EUS-guided celiac plexus neurolysis (EUS-CPN) for pancreas cancer pain management [8, 127–129]
EUS-guided placement of fiducial markers to aid image guided radiation therapy [8, 130–132]
EUS-guided tattoo injection for intraoperative localization of pancreatic tumors [8, 133]
EUS-guided biliary drainage (choledochoduodenostomy or hepaticogastrostomy) or EUS assisted ERCP (rendezvous) [134]
EUS-guided gastroenterostomy for management of malignant gastric outlet obstruction [135–138]
EUS-guided direct therapies such as radiofrequency ablation or injection of ablative agents [139–141]
EUS-guided delivery of chemotherapy, immunotherapy, or other experimental vectors [132]

Conclusion

Since its inception almost 30 years ago, EUS has evolved from an alternative investigational tool to a primary contributor for several aspects of care for the pancreatic cancer patient. Awareness of the variables affecting sampling, refinements of technique, new accessories, and incorporation of evidence-based best practice will continue to improve outcomes. Advances in EUS technology hold promise for continued improvement and expanded applications of this procedure especially with respect to molecular analysis of EUS-FNA/FNB aspirate and innovative treatments.

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4. Endoscopic Ultrasound (EUS) Market Size, Share & Industry Analysis, By Product (Endoscopes (Radial Endoscopes and Linear Endoscopes), Ultrasound Probes, Ultrasonic Processors, Imaging Systems, Needles, and Accessories) By Application (Oncology Pancreatic Conditions, and Others), By End User (Hospitals, Ambulatory Surgery Centers, Others) and Regional Forecast 2019–2026 2019 [Available from: https://www.fortunebusinessinsights.com/industry-reports/endoscopy-ultrasound-market-100558.
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8 Diagnosis and Staging of Pancreatic Cancer: Role of Ca 19-9 in Diagnosis/Staging and Management

Adrianne Tsen and Manoop S. Bhutani

Since its discovery in 1979, carbohydrate antigen 19-9 (CA 19-9) has become the most widespread tumor biomarker used in the diagnosis and management of patients with pancreatic cancer. Despite the various potential pancreatic tumor biomarkers available, none has been more extensively studied and validated than CA 19-9. In this section we will discuss the role of CA 19-9 in diagnosis, staging, and management of pancreatic adenocarcinoma.

Normal range of CA 19-9 levels is between 0 and 37 U/mL. The usefulness of this tumor-associated antigen greatly depends on the situation. As a screening tool in asymptomatic patients, CA 19-9 levels have been shown to have poor predictive value and routine measurement is not recommended in clinical practice. For patients with symptoms suspicious of pancreatic cancer, elevated CA 19-9 has also been shown to be a poor predictor with a predictive value of 0.5–0.9% [1]. Similarly, in patients with small tumors or with early stages of the disease, CA 19-9 cannot be recommended as a screening tool due to its low sensitivity (~80%) and specificity (~80%) [2].

However, in patients who present with a pancreatic mass, elevated CA 19-9 has a much higher predictive value. As demonstrated by Tessler et al in a study of 150 patients, when elevated CA 19-9 levels >37 U/mL are combined with unintentional weight loss of >20 lbs and total bilirubin ≥3 mg/dL in patients presenting with a pancreatic mass, specificity of CA 19-9 increases to nearly 100% for pancreatic cancer regardless of the extent of imaging abnormalities [1]. Overall, elevated CA 19-9 has a sensitivity and specificity of 79–81% and 80–82%, respectively, in diagnosing pancreatic adenocarcinoma in symptomatic patients.

A caveat in which elevated CA 19-9 must be carefully interpreted is in the presence of obstructive jaundice. Several retrospective reviews and meta-analyses have revealed that in cases of hyperbilirubinemia secondary to obstructive jaundice, CA 19-9 is unreliable in distinguishing between benign and malignant pancreaticobiliary diseases. The mechanisms by which CA 19-9 is falsely elevated in obstructive jaundice are not well understood but it is theorized that increased production of the tumor-associated antigen by cholangiocytes is primarily responsible. In biliary obstruction, increases in biliary ductal pressure are thought to "irritate" cholangiocytes, thereby resulting in increased secretion of CA 19-9. This irritation results in inflamma-

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_8

tory proliferation of CA 19-9, which when combined with decreased clearance of CA 19-9 due to the obstruction causes leakage of CA 19-9 into systemic circulation and ultimately, false elevations in CA 19-9. Therefore, elevations of CA 19-9 in cases of biliary obstruction should be interpreted with caution.

For patients presenting with a pancreatic mass without biliary obstruction, it is well established that elevated CA 19-9 levels not only confer a high predictive value for diagnosing pancreatic carcinoma but significantly affect clinical decisions regarding treatment. CA 19-9 provides a rough estimate of tumor biology and aggressiveness and in recent years has become part of the broader definition for determining resectability. Preoperative CA 19-9 levels have been studied as potential surrogate markers for tumor resectability. Although an optimal cutoff is not well established, preoperative CA 19-9 levels >150 U/mL carry an 88% positive predictive value for determining unresectability, and levels <150 U/mL carry a negative predictive value of 64% [1]. Other studies have shown that a median CA 19-9 level < 100 U/mL correlates with a 41–80% chance of resectability, while levels >100 U/mL suggest advanced or metastatic disease [1]. Unsurprisingly, 96% of tumors with CA 19-9 levels >1000 U/mL are found to be unresectable [3].

The International Association of Pancreatology utilizes CA 19-9 in their definition of borderline resectability—locally resectable tumors are categorized as borderline resectable once CA 19-9 levels are greater than 500 U/mL or regional lymph node metastases are found [4]. Accordingly, these elevated CA 19-9 levels play a pivotal role as completion of adjuvant therapy following major pancreatic surgery is unlikely [4]. As such, in the presence of high CA 19-9 levels, treatment of choice for borderline resectable pancreatic adenocarcinoma becomes neoadjuvant therapy [4].

In one of the largest retrospective cohort studies, Mirkin et al. further evaluated the relationship of pre-treatment CA 19-9 levels taken at diagnosis with overall survival [5]. Data of 4701 patients with stage I-III disease from the National Cancer Database were reviewed [5]. The primary outcome assessed was survival. Among the 4701 patients, 592 patients received neoadjuvant therapy, 1286 patients underwent surgically resection, and 2823 patients received surgical resection and adjuvant chemotherapy [5]. Results revealed no association between pre-treatment CA 19-9 levels ≤ 800 U/mL and survival at any stage for patients who underwent surgical resection with or without adjuvant therapy [5]. However CA 19-9 levels >800 U/mL did correlate with worse survival among all clinical stages [5]. Similarly, for patients who received neoadjuvant therapy with surgery, no association of CA 19-9 levels ≤800 U/mL was seen in stage I or II disease [5]. Pre-treatment CA 19-9 levels >800 U/mL were significantly associated with worse survival in stage I but not stage II or III disease, demonstrating a survival benefit in these patients who receive neoadjuvant therapy [5]. This study overall demonstrated that pre-treatment CA 19-9 levels >800 U/mL are associated with advanced stage of disease and worse survival in all clinical stages [5].

Perhaps the most established and greatest clinical value of CA 19-9 is when used as a means to prognosticate survival and recurrence following surgical resection. Multiple studies have confirmed that following surgical resection, patients who normalize their CA 19-9 levels postoperatively have longer survival than those who do not [3]. Given the half-life of 14 h, it is recommended that CA 19-9 levels be obtained 4–6 weeks following surgery. As a general consensus, CA 19-9 levels <37 U/mL or low preoperative CA 19-9 levels <100 U/mL correlate with early stage of disease and independently predict overall survival [1]. CA 19-9 levels which fail to normalize are attributed to residual disease or occult metastasis and portend a poor overall survival [1]. Additionally, alterations in CA 19-9 levels may be useful in identifying micrometastatic lesions following surgical resection [6].

Several trials have demonstrated survival benefit for patients who receive neoadjuvant therapy and particularly in those who receive neoadjuvant chemotherapy, CA 19-9 has been found to correlate with recurrence and survivability. Similar to those who are surgically resected,

patients who normalize their CA 19-9 levels following neoadjuvant therapy hold a more favorable prognosis and lower incidence of hepatic recurrence [6]. Furthermore, for patients who exhibit a favorable response to neoadjuvant chemotherapy but whose CA 19-9 levels remain above normal, several additional cycles of neoadjuvant therapy may be administered until CA 19-9 normalization, thereby resulting in increased survivability and lower recurrence rates following surgical resection [6].

Measurement of CA 19-9 levels after induction chemotherapy also appears to be of use in determining which patients would benefit from exploratory surgery. Induction chemotherapy with FOLFIRINOX in patients with locally advanced pancreatic cancer may lead to downstaging and in 20–25% of cases result in surgically resectable disease [7]. Determining which tumors meet resectability criteria, however, may not always be clear. Following induction chemotherapy, treatment response and resectability are typically assessed with CT-imaging using the Response Evaluation Criteria in Solid Tumors (RECIST1.1) [7]. In patients who meet RECIST-stable disease, defined as having lack of tumor progression or regression, one of the challenges of CT-imaging is inability to distinguish between fibrotic versus viable tumor tissue [7]. As a result, patients with RECIST-stable disease do not undergo surgical exploration since negative surgical explorations in pancreatic cancer are associated with poorer outcomes [7].

In a small study of 54 patients who underwent induction chemotherapy, Van Veldhuisen and colleagues demonstrated that when combined with criteria meeting RECIST-regression, a decrease of ≥30% in CA 19-9 levels improved the sensitivity, positive predictive value, and negative predictive value for determining resectability [7]. Based on these results, they postulate that measurement of post-induction chemotherapy CA 19-9 levels may be beneficial in determining resectability in patients with RECIST-stable disease. Further studies with a larger patient population, however, are still needed.

CA 19-9 continues to be used as a surrogate marker of overall response and survival to new experimental therapies. A new strategy in approaching patients with locally advanced or initially unresectable pancreatic cancer, termed "adjuvant surgery," has gained momentum in recent years due to studies reporting improved overall survival for highly selective patient populations who respond favorably to multimodal treatments [6]. Patients who qualify for adjuvant surgery do so after receiving nonsurgical anticancer treatments for more than 240 days, maintain CA 19-9 levels within a relatively low range, and do not show progression or development of occult distant metastasis following various treatment modalities or surgical exploration [6]. Another novel treatment, irreversible electroporation (IRE), a nonthermal ablative technique, has emerged as a potential treatment option for patients with locally advanced pancreatic cancer and measurement of CA 19-9 levels is used to monitor treatment response. In a small multicenter, prospective study of 40 patients with locally advanced pancreatic cancer and 10 isolated local recurrence following surgical resection subsequently treated with IRE, elevated CA 19-9 levels corresponded to poorer survival [8]. CA 19-9 levels >2000 U/mL before IRE and ≤50% reduction in CA 19-9 levels 3 months following IRE were associated with worse overall survival [8].

It is important to remember that pancreatic adenocarcinoma is not the only malignancy with elevated levels of CA 19-9 in the serum. Other cancers that can increase this marker in the serum include cholangiocarcinoma, gall bladder cancer, ampullary carcinoma, hepatocellular carcinoma, gastric cancer, ovarian cancer, colorectal cancer, lung cancer, breast cancer, endometrial cancer, and thyroid cancer.

Furthermore, there are many benign conditions associated with increased CA 19-9 including but not limited to benign biliary stricture, acute cholangitis, Mirrizzi's syndrome, choledocholithiasis, gall stones, acute cholecystitis, acute pancreatitis, primary biliary cirrhosis, hepatic cysts, acute and chronic hepatitis, bronchiectasis, interstitial lung disease, cystic fibrosis, endometriosis, and uncontrolled diabetes mellitus. Furthermore, CA 19-9 is cleared through the

kidney and levels can be elevated with chronic kidney disease and reduced glomerular filtration rate. There are also some individuals with elevated CA 19-9 where there is no apparent cause. Thus, it is important to check and interpret serum CA 19-9 level in the right clinical context.

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Part II

Management of Locally Advanced/Metastatic Disease

9 Management of Locally Advanced/Metastatic Disease: Medical Oncology

Jonathan D. Mizrahi and Robert A. Wolff

Introduction

Up to 85% of patients with pancreatic cancer have unresectable disease at the time of diagnosis, either due to local tumor invasion or metastatic spread. As is the case for many other solid tumors, cytotoxic chemotherapy remains the mainstay of treatment for this group of patients. Goals of systemic therapy include prolongation of survival and palliation of symptoms. Occasionally, patients with locally advanced disease may become eligible for surgical resection after initial systemic therapy. Improvements in chemotherapy regimens over the past decade have led to important, albeit modest, gains in the survival of patients with advanced pancreatic cancer. Below we will review treatment approaches from the medical oncology perspective for patients with locally advanced and metastatic disease.

Locally Advanced Disease

Approximately one-third of patients present with unresectable, locally advanced disease at the time of diagnosis with pancreatic cancer. While several definitions of the stages of resectability have been developed over the past decade and a half, each centers on the relationship between the tumor and surrounding vasculature [1–3]. The MD Anderson Criteria for resectability for pancreatic cancer define locally advanced disease as tumors that either encase the superior mesenteric artery, the celiac axis, or hepatic artery without a reconstructive option or occlude the superior mesenteric or portal veins without a reconstructive option (Fig. 9.1) [2].

Given the contraindication to surgery and the high probability of occult metastatic disease in this population, systemic chemotherapy is the

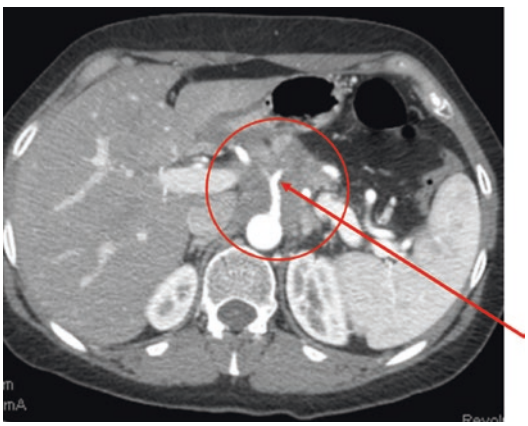

Fig. 9.1 Locally advanced pancreatic cancer. Tumor arising from head and body of pancreas is circled. Arrow indicates celiac artery which is being encased by tumor, rendering it unresectable

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_9

recommended first-line treatment in patients with locally advanced pancreatic cancer (LAPC). The GERCOR group retrospectively analyzed patients with LAPC treated in their trials with first-line chemotherapy, which was either 5-fluorouracil (5-FU) + leucovorin + gemcitabine or gemcitabine + oxaliplatin [4]. They found that 29% of patients developed disease progression during the first 3 months of chemotherapy, a subset that had a median overall survival of 4.5 months. This data highlights the heterogeneity in aggressiveness of LAPC. Upfront systemic therapy identifies patients with particularly aggressive biology as those who would not benefit from local therapy such as radiation.

Guidelines on the optimal initial chemotherapy regimen for patients with LAPC rely primarily on data from patients with metastatic disease. Combination regimens such as FOLFIRINOX and gemcitabine + nab-paclitaxel are frequently utilized in this setting, owing to their proven efficacy in phase 3 studies of patients with metastatic pancreatic cancer [5, 6]. A 2016 systematic review evaluated the role of FOLFIRINOX in LAPC in 315 patients across 11 studies [7]. The authors reported a median overall survival of 24.2 months (95% CI 21.7–26.8) and median progression-free survival (PFS) of 15.0 months (95% CI 13.8–16.2). The pooled proportion of patients with LAPC who underwent resection was 25.9%, with 78.4% having an R0 (microscopically negative) resection.

Gemcitabine-based combination regimens also have limited data in the locally advanced setting. A phase 2 study in Austria evaluated gemcitabine + oxaliplatin as "neoadjuvant" therapy in patients with LAPC [8]. Of the 33 patients in their study, 13 underwent resection with a 69% R0 resection rate. The patients who underwent resection had a median OS of 22 months, compared to 12 months for those who did not undergo resection. An important caveat to these results is that 15 of the 33 patients were considered to have borderline resectable disease at the time of diagnosis when evaluated by centralized imaging review. The results of the multicenter phase 2 LAPACT trial which evaluated the combination of induction gemcitabine + nab-paclitaxel in patients with LAPC were reported in 2018 [9]. One hundred seven patients were included in the study, and the median PFS was 10.2 months. Neutropenia was the most common (42%) grade 3 or 4 adverse event, but the authors found the regimen to be largely tolerable. Sixteen patients (15%) in this study underwent surgical resection with 7 having an R0 resection.

For patients who are not eligible for combination chemotherapy regimens due to comorbidities or poor performance status, single agent gemcitabine is a reasonable alternative. Evidence for the use of gemcitabine monotherapy in this setting is largely extrapolated from older clinical trials that included patients with LAPC and metastatic disease [10–12]. Results published from the LAP07 trial, which studied the benefit chemoradiation compared with continuation of chemotherapy in patients with LAPC, demonstrated that induction chemotherapy with single agent gemcitabine resulted in a median overall survival of 13.6 months [13]. Radiotherapy with or without concurrent chemotherapy is another first-line option for patients who cannot tolerate combination chemotherapy, an approach that will be discussed later.

Despite improvements in response rates with combination chemotherapy, most patients who are initially considered to have LAPC never become candidates for curative surgical resection. However, patients who demonstrate response to induction systemic therapy without the development of overt metastatic disease should be re-evaluated for the possibility of resection by an experienced multi-disciplinary team. This is an approach supported by both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) [14, 15]. A study of 415 patients with LAPC treated at Johns Hopkins from 2013 to 2017 found that 84 (20%) underwent surgical resection after a median of 5 months of pre-operative therapy. Median OS was higher in the resected cohort at 35.3 months, compared to 16.3 months in the non-resected patients. They also found that the use of FOLFIRNOX and ste-

reotactic body radiation therapy (SBRT) was associated with an increased probability of surgical resection.

The German phase 2 NEOLAP study randomized 130 LAPC patients at 33 different institutions who had not progressed on 2 initial cycles of gemcitabine + nab-paclitaxel to either continue the doublet for 2 more cycles or switch to 4 cycles of FOLFIRINOX [16]. The study's results, presented in 2019, included a primary endpoint of conversion rate to resectability. The conversion rate in the gemcitabine + nab-paclitaxel group was 30.6%, compared to 45.0% in the FOLFIRINOX group (p = 0.135). Median OS was not different between the two chemotherapy arms, but conversion to resectability was associated with an improved median OS (27.4 vs 14.2 months, p = 0.0035).

Determining a patient's potential for downstaging and future resectability at the time of diagnosis with LAPC is very challenging. An attempt has been made by clinicians at the Medical College of Wisconsin to categorize LAPC patients into "type A" (potentially resectable) or "type B" (very likely not resectable) based on vascular involvement and the potential for surgical resection after neoadjuvant therapy [17]. An analysis of 108 consecutive patients with LAPC who were categorized into type A or B under this schema found that 62% of type A and 24% of type B patients underwent surgical resection [18]. The authors concluded that such a classification may help establish appropriate expectations and goals of care with patients.

Patients who continue to have stable but unresectable disease after induction chemotherapy of 4 to 6 months should be considered for either continuation of systemic therapy, a treatment break, or consolidative chemoradiotherapy. This decision should be made taking into account the patient's goals of care, performance status, and symptoms. ASCO and NCCN guidelines recommend observation for this population in the absence of a clinical trial. For patients who are treated with chemoradiotherapy, there may be some benefit to maintenance systemic chemotherapy if their disease continues to be localized [19].

The role of radiation therapy in locally advanced disease will be discussed in greater depth later in this chapter. For LAPC patients who are treated with radiation, the addition of concurrent chemotherapy as a sensitizing agent has become commonplace. A 2009 systematic review analyzed the benefits of chemoradiotherapy in 21 published studies and concluded that chemoradiotherapy increases OS compared to radiotherapy alone, at the cost of higher toxicity [20]. The SCALOP trial was a randomized phase 2 study comparing gemcitabine-based chemoradiotherapy to capecitabine-based chemoradiotherapy for patients who had not developed disease progression during 12 weeks of induction chemotherapy with the combination of gemcitabine and capecitabine [21]. Seventy-four LAPC patients were ultimately randomized to one of the chemoradiotherapy groups in the study, and median OS was improved with capecitabine compared to gemcitabine (15.2 vs 13.4 months, hazard ratio [HR]: 0.39, p = 0.012). The adverse effect profile also favored capecitabine-based chemoradiotherapy, though quality of life scores were not different between the arms.

Metastatic Disease

The medical management of a patient with metastatic pancreatic cancer is frequently complex and often requires attention to pain control, thromboembolic disease, biliary or gastrointestinal obstruction, infection, pancreatic exocrine insufficiency, and anorexia/weight loss, in addition to side effects from chemotherapy (Fig. 9.2). However, administration of chemotherapy has been shown to have the dual benefit of prolonging survival and improving quality of life [22, 23]. The two most commonly utilized first-line chemotherapy regimens are FOLFRINOX and gemcitabine + nab-paclitaxel (Table 9.1).

FOLFIRINOX was established as a standard-of-care first-line regimen based on data from the large phase 3 study conducted by Conroy et al. comparing the combination with gemcitabine monotherapy, the previous standard-of-care [5]. A total of 342 patients with metastatic pancreatic

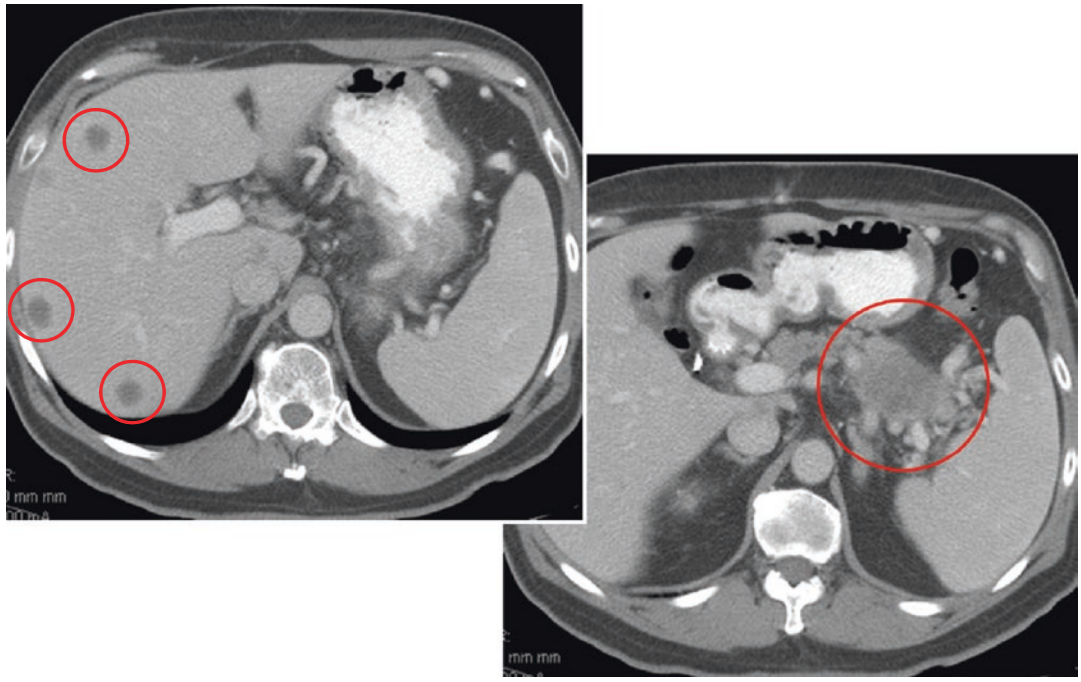

Fig. 9.2 Metastatic pancreatic cancer. Left: CT image of hypodense liver lesions consistent with metastatic spread (circled). Right: CT image of tumor arising from tail of pancreas (circled). Patients with tumors of the pancreatic tail often present with metastatic disease

Table 9.1 First-line chemotherapy regimens for metastatic pancreatic cancer

Drug	Response rate (%)	Median survival	1 year survival rate (%)
Gemcitabine	10	2.7 months	18
Gemcitabine/Erlotinib	8	6.4 months	24
Gemcitabine/nab-p	22	8.3 months	24
FOLFIRINOX	32	11.1 months	48

Nab-p nanoalbumin-bound paclitaxel, *FOLFIRINOX* 5-Fluorouracil + leucovorin + irinotecan + oxaliplatin

cancer were randomized to either FOLFIRINOX or gemcitabine. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate liver and renal function. Compared to gemcitabine, FOLFIRINOX improved median OS (11.1 vs 6.8 months, HR, 0.57, $p < 0.001$). The FOLFIRINOX arm also demonstrated an improved objective response rate (31.6% vs 9.4%) and median PFS (6.4 vs 3.3 months, HR, 0.47, $p < 0.001$). Importantly, rates of grade 3 or 4 adverse events were higher in the FOLFIRINOX group, including neutropenia (45.7% vs 21.0%) and diarrhea (12.7% vs 1.8%).

Two years after the data on FOLFIRINOX was published, the results of the phase 3 MPACT trial were published, comparing gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) to gemcitabine monotherapy in 861 patients. Similar to FOLFIRINOX, this doublet improved median OS compared to gemcitabine (8.5 vs 6.7 months, HR, 0.72, $p < 0.001$). Median PFS was 5.5 months with gemcitabine + nab-paclitaxel compared to 3.7 months for the single agent (HR: 0.69, $p < 0.001$). As expected, grade 3 or 4 adverse effects were higher in the doublet arm including neutropenia (38% vs 27%), fatigue (17% vs 7%), and neuropathy (17% vs 1%).

The selection of which first-line chemotherapy, if any, to utilize depends on patient comorbidities and performance status. For patients with an excellent performance status, either regimen is appropriate. Most clinicians consider gemcitabine + nab-paclitaxel to be a more tolerable therapy and may recommend the doublet for a patient with a borderline performances status. Single agent gemcitabine represents another option for patients whose performance status or comorbidities preclude a combination regimen [10, 24]. Comorbid conditions such as preexisting peripheral neuropathy may necessitate treatment that omits platinum or taxanes, such as FOLFIRI or gemcitabine alone. Additionally clinicians should be cautious about prescribing irinotecan and potentially gemcitabine in patients with hepatic impairment. Despite a cutoff of 75 years in the pivotal 2011 study leading to the approval of FOLFIRINOX, age, alone, should not necessarily dictate which first-line chemotherapy is selected, as performance status is often a better predictor of tolerability [25].

Patients who maintain an ECOG performance status of ≤ 2 may be considered for second-line therapy. NAPOLI-1 was a phase 3 study of second-line therapy in 417 patients with metastatic pancreatic cancer whose disease had progressed on gemcitabine-based chemotherapy [26]. Patients were randomized to one of the three arms: (1) 5-FU + leucovorin, (2) nanoliposomal irinotecan, or (3) combination of 5-FU + leucovorin + nanoliposomal irinotecan. The primary endpoint, median OS, in the 5-FU + leucovorin + nanoliposomal irinotecan group was 6.1 months compared to 4.2 months in the 5-FU + leucovorin group (HR: 0.67, $p = 0.012$). These results led to the approval of 5-FU + leucovorin + nanoliposomal irinotecan as a second-line regimen for gemcitabine-refractory patients in 2015. For patients who were treated with first-line 5-FU-based therapy, including FOLFIRINOX, gemcitabine + nab-paclitaxel represents a reasonable option for eligible patients, despite limited prospective data [27, 28]. Many patients who progress on first-line therapy are not candidates for further systemic therapy and should be managed with best supportive and/or hospice care.

Incorporation of targeted therapies into the armamentarium of pancreatic cancer treatment has largely been ineffective. A mutation in the *KRAS* gene is an almost universal finding in pancreatic cancers, and its subsequent activation is a well-described driver of pancreatic tumor development [29–32]. Despite decades of effort by researchers from the bench to clinic, the discovery of an effective therapy to target this crucial oncogene has been elusive thus far [33, 34]. Downstream to *KRAS* are potential therapeutic targets including mTOR, RAF, MEK, though inhibition of these proteins in pancreatic cancer patients has not demonstrated clinical efficacy in multiple clinical trials [35–39]. The addition of monoclonal antibodies targeting VEGF and EGFR to gemcitabine chemotherapy has similarly shown no benefit in large phase 3 clinical trials [40, 41]. One notable exception is erlotinib, an oral tyrosine kinase inhibitor with activity against EGFR, which demonstrated a statistically significant improvement in OS when added to gemcitabine compared to gemcitabine alone in a randomized phase 3 study [42]. However, erlotinib is seldom utilized in clinical practice as its addition to gemcitabine improved median OS by fewer than 2 weeks, and it is associated with nontrivial toxicities.

One targeted strategy with recent therapeutic success aims to exploit aberrancies in DNA damage repair pathways. While germline mutations in *BRCA1* and *BRCA2* are found in only up to 7%, broadening the umbrella of DNA damage repair mutations to include genes such as *PALB2*, *ATM*, *RAD51*, and *CHEK1/2* may increase this population to almost a quarter of patients with pancreatic cancer [30, 43–48]. Patients with aberrant DNA damage repair are more susceptible to DNA-damaging therapies, including platinum chemotherapy as well as radiation. More recently, the development of inhibitors of poly(adenosine diphosphate-ribose) polymerase (PARP), a crucial component of the homologous recombination pathway for single-strand DNA breaks, has offered a novel therapeutic agent. Phase 2 studies

of the PARP inhibitors olaparib and rucaparib as single agents have shown promising activity in pre-treated pancreatic cancer patients with germline or somatic *BRCA1* and *BRCA2* mutations [49, 50]. The phase 3 POLO trial randomized 154 metastatic pancreatic cancer patients with germline *BRCA1* or *BRCA2* mutations whose disease had not progressed on at least 16 weeks of first-line platinum-based chemotherapy to either maintenance placebo or olaparib [51]. The median PFS in the olaparib group was significantly longer (7.4 vs 3.8 months, HR: 0.53, $p = 0.004$). At the interim analysis, there was no difference in overall survival between the groups. In December 2019, olaparib was granted FDA approval for this indication, marking the first biomarker-based targeted therapy approved for pancreatic cancer [52]. Another rare but clinically significant molecular aberration is a fusion in the *NTRK* gene, which occurs in up to 1% of patients with pancreatic cancer and has been demonstrated in case reports to be a clinically significant target with the inhibitor, entrectinib [53]. In 2019, the FDA approved entrectinib as a tumor-agnostic treatment for patients with advanced solid tumors harboring *NTRK* fusions [54]. Tumor molecular profiling that includes evaluation for *NTRK* gene fusions should be considered for patients with advanced pancreatic cancer.

Over the past several years, immunotherapy has completely changed the treatment landscape in a number of malignancies including melanoma, non-small cell lung cancer, and genitourinary cancer. Unfortunately, most patients with gastrointestinal cancers have not reaped these benefits. Pancreatic cancer, in particular, has repeatedly failed to demonstrate response to single agent immune checkpoint inhibition outside of the approximately 1% of patients whose tumors harbor mutations in mismatch repair proteins or have high microsatellite instability (MSI-H) [55–59]. It has been hypothesized that immunotherapy in pancreatic cancer fails based on the presence of an immunologically "cold," immunosuppressive, tumor microenvironment with abundant tumor-associated macrophages, regulatory T cells, cancer-associated fibroblasts, and myeloid-derived suppressor cells [60–62]. Clinical studies aiming to introduce cytotoxic lymphocytes or target these immunosuppressive components of the pancreatic tumor microenvironment in order to enhance the activity of both chemotherapy and immune checkpoint inhibitors are ongoing (e.g. NCT03336216, NCT02588443).

The treatment of patients with advanced pancreatic care invariably requires clinicians to incorporate supportive care. Common symptoms include pain, nausea, diarrhea, depression, anxiety, anorexia, and weight loss. Early recruitment of supportive or palliative care specialists to the treatment team can reduce the complexity of management by oncologists and has been demonstrated to decrease the aggressiveness of care near the time of death [63]. Pain is a near universal symptom, and its etiology is often multifactorial owing to local invasion into the celiac plexus or effects of distant metastases. Opioid-based therapy is the recommended treatment of cancer-related pain, but interventions such as celiac plexus neurolysis are also commonly utilized [64]. Biliary obstruction is another common effect of pancreatic cancer that can lead to infection and often precludes adequate delivery of chemotherapy. When required, biliary stenting with metal rather than plastic stents tends to improve stent patency and lowers infection risk [65]. Antidepressants, appetite stimulants, antiemetics, and pancreatic enzyme replacements are all part of the armamentarium of clinicians and should be considered for appropriate patients.

Approach to LAPC at MD Anderson

While an individualized approach is necessary for patients with locally advanced, unresectable disease, the general approach at MD Anderson Cancer Center is to begin with systemic therapy. FOLFIRINOX is typically given to patients with good performance status and no contraindications to treatment with oxaliplatin, such as pre-existing peripheral neuropathy. For those patients with frailty or comorbidities, gemcitabine and nab-paclitaxel given once every 2 weeks (rather than weekly × 3, every 28 days) are more com-

monly utilized. Restaging evaluations consisting of routine laboratory studies and serum tumor markers in addition to contrast-enhanced computed tomography of the chest, abdomen, and pelvis are performed every 2 months. If a patient develops metastatic disease or progression of the primary tumor with first-line chemotherapy, second line chemotherapy is usually recommended with efforts to enroll such patients on active clinical trials. For the subset of patients who have not progressed after 4–6 months of systemic therapy, referral to a radiation oncologist to consider consolidating radiation therapy is advised. Whenever possible, delivery of consolidating radiation is conducted in the context of a clinical trial. Importantly, the smaller subset of patients who have a clinical and radiographic response to chemotherapy with or without radiation at the primary tumor site without interval metastatic disease should be referred to an experienced surgical oncologist to consider surgical resection with curative intent. This is particularly true of those patients who have normal or near-normal serum tumor markers after systemic therapy ± radiation.

MD Anderson Approach to Metastatic Pancreatic Cancer

Combination chemotherapy is the most common recommendation for patients who present with metastatic disease. The choice of FOLFIRINOX or gemcitabine and nab-paclitaxel is based on the individual patient's personal wishes, performance status, comorbidities, and frailty. FOLFIRINOX is usually preferred as first-line therapy for patients with ECOG performance status 0–1. Gemcitabine and nab-paclitaxel are more commonly offered to those patients with ECOG performance status 1–2. In some cases, only gemcitabine monotherapy should be considered, particularly for patients with frailty or those likely to experience increased toxicity with combination therapy (Table 9.2). When feasible, enrollment in a front-line clinical trial is considered, especially for patients with well-preserved performance status.

Table 9.2 Association between performance status and survival in pancreatic cancer

Karnofsky performance status (%)	Median survival (months)
70	3.9
80	8.1
90	8.9
100	12.6

Tabernero J, et al. Oncologist 2015

Whenever possible, germline genetic testing and molecular profiling of biopsy material are recommended to identify patients who may benefit from subsequent targeted therapy, most commonly olaparib for patients with germline BRCA mutations delivered as maintenance therapy. This is usually appropriate after 4–6 months of cytotoxic therapy with a platinum agent such as oxaliplatin. Clinical trial enrollment is considered for patients with progressive disease after front-line therapy who maintain good performance status. Importantly, attention to the results of germline testing and/or molecular profiling of biopsy material for enrollment in biomarker-specific clinical trials is strongly encouraged.

Conclusion

Patients with locally advanced or metastatic disease comprise the overwhelming majority of those with pancreatic cancer. Cytotoxic chemotherapy continues to be the only treatment that offers a clear survival benefit for this group of patients. The development of combination chemotherapy regimens over the past decade, particularly gemcitabine + nab-paclitaxel and FOLFIRINOX, has extended the life expectancy of most patients with advanced disease. While a small percentage of initially locally advanced pancreatic cancers may ultimately become surgically resectable, the goal of therapy in the vast majority of patients is palliative in nature. Improvements in biomarker selection and novel targeted agents have already begun to expand therapeutic options for a minority of patients such as those with germline *BRCA1/2* mutations, and there is optimism for similar future successes

in other pancreatic cancer patients. While immune checkpoint inhibitors largely have no role in pancreatic cancer, manipulation of the immunosuppressive tumor microenvironment appears necessary to unlock the therapeutic potential of immunotherapy in this disease. Finally, supportive care is a crucial, if underappreciated, component of care for patients with advanced pancreatic cancer.

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10 Management of Locally Advanced/Metastatic Disease: Radiation Oncology

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Introduction

Pancreatic cancer is known to be one of the most aggressive forms of cancers, with a cumulative 5-year overall survival of around 9% [1]. Moreover, recent statistics from the American Cancer Society show that the incidences of pancreatic cancer and pancreatic cancer mortality are still increasing [1]. This is partly due to the vague initial presentations and symptomatology of pancreatic cancer, along with the absence of proper screening tools. As such, around one-third of patients with pancreatic cancer present with locally advanced disease [2]. Locally advanced pancreatic cancer (LAPC) is defined as any pancreatic cancer that is neither resectable nor metastatic. Such disease carries a poor prognosis, with a median overall survival of 9 to 11 months [3, 4]. With much debate on the best treatment modality for LAPC, sequencing of chemotherapy and radiation therapy, as well as chemotherapy regimens and radiation therapy techniques, optimal treatment for such cases is still not established. In these patients, the main goals of therapy are to improve local control and prevent distant progression of disease, in the hope of improving overall survival and quality of life. Since surgical management is not an option, the prognosis of these patients remains poor and depends highly on the combination of chemotherapy and radiotherapy combination. While chemotherapy addresses the issue of distant spread, radiation therapy focuses mainly on controlling the disease locally. In patients with LAPC, local control is crucial, as around 30% of patients with pancreatic cancer die from local disease without developing distant metastases [5]. In this chapter, we review the role of radiation therapy with its different modalities in the management of locally advanced pancreatic cancer.

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Radiation Therapy Treatment Strategies for Unresectable Disease

Chemoradiation

Treatment with a combination of chemotherapy and radiation therapy is common among patients with LAPC. However, clinical outcomes remain

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_10

non-satisfactory, and treatment optimization is still warranted.

A prospective randomized trial was published by Shinchi et al. in 2002 and showed that patients who received chemoradiotherapy had better overall survival and quality of life when compared to patients who only received best supportive care [6]. Additionally, some evidence shows that the use of concurrent chemoradiotherapy might be superior to the use of radiotherapy alone. An old study by the Gastrointestinal Tumor Study Group analyzed survival among LAPC patients who received concurrent chemoradiotherapy with 5-FU and either low or high dose radiation therapy, and patients that only received high dose radiation therapy [7]. The study showed improved overall survival in patients who received concurrent chemoradiotherapy (60 Gy + 5-FU 1-year overall survival: 46%), versus those who received high dose radiotherapy alone (60 Gy 1-year overall survival: 10%) [7]. Following this study, a more recent phase III trial was conducted and published by the Eastern Cooperative Oncology Group in 2005 [8]. The trial compared patients receiving high dose radiotherapy alone to patients receiving radiation therapy with additional 5-FU and mitomycin treatment. The results of the study showed increased toxicity in the chemoradiation arm, with no improvement in overall and disease-free survival [8].

Furthermore, comparing chemoradiotherapy to chemotherapy alone shows mixed results. While data from the Gastrointestinal Tumor Study Group offers some survival benefits with the addition of radiation therapy to 5-FU chemotherapy, other studies report similar outcomes between those groups [9–11]. Furthermore, data from the 2000–2001 FFCC/SFRO study randomized patients to either receive induction chemoradiotherapy with 5-FU and cisplatin or receive induction gemcitabine alone [12]. Both arms subsequently received gemcitabine for maintenance until disease progression or toxicity. Results from this study actually showed better outcomes in the gemcitabine arm, with improved survival rates and less toxicities [12]. On the other side, the Eastern Cooperative Oncology Group compared the use of gemcitabine alone or in combination with radiation therapy and showed that the use of chemoradiotherapy was associated with better survival rates (chemoradiotherapy: median survival of 11.1 months vs chemotherapy: median survival of 9.2 months) [13]. Finally, the recent LAP 07 trial compared chemoradiotherapy (54 Gy + Capecitabine) versus chemotherapy alone (gemcitabine or gemcitabine and erlotinib) in patients that already received chemotherapy (either gemcitabine or gemcitabine and erlotinib) [14]. The results show improved local control in the chemoradiotherapy arm, but no survival benefit to the addition of radiation therapy. Nevertheless, this study used gemcitabine-based chemotherapy, rather than FOLFIRINOX which might limit the applicability of the results to current FOLFIRINOX-based regimens [14].

All of the following studies give some insight into the role of chemoradiation in locally advanced pancreatic cancer. However, most studies analyzed only a small number of patients. Also, most studies are relatively old and do not account for recent radiation and chemotherapy advances. Based on the following, the benefit of chemoradiation remains controversial, and an ideal chemoradiation protocol for LAPC is still not established.

At the MD Anderson Cancer Center, our approach is to first treat LAPC patients with neoadjuvant chemotherapy for around 2 to 6 months (Fig. 10.7). There are two major chemotherapy regimens: FOLFIRINOX and gemcitabine/nab-paclitaxel. There is no consensus on which regimen to use, but typically FOLFIRINOX is the first choice. Patients with contraindications or lower performance status may be started on gemcitabine and nab-paclitaxel. We typically follow up with the patient and a multidisciplinary team every 2 months, with repeat imaging and blood work-up. Chemotherapy is continued as long as the patient is responding by CA19-9 decrement or by radiologic improvement. If the patient's tumor stops responding to treatment, the chemotherapy regimen is often switched [15]. Although pancreatic tumors do not often downstage with chemotherapy alone, there are case reports of occasional excellent responders whose tumor

may be resectable after initial chemotherapy [16, 17]. Thus, after sufficient chemotherapy and stabilization of the tumor and CA19-9, we then consider definitive concurrent chemoradiation. A commonly used approach is the use of chemotherapy along with the delivery of hypofractionated IMRT, typically 67.5 Gy in 15 fractions [18]. The use of escalated dose radiation—defined as a biological equivalent dose of 70 Gy or higher—with IMRT planning yielded improved local-regional control and overall survival when compared to standard dose radiation (50.4 Gy/28 fractions) with concurrent chemotherapy [19, 20]. Hypofractionated IMRT also showed improved tolerability, with less gastrointestinal and overall toxicities. Another promising regimen is the use of IMRT to a dose of 75 Gy in 25 fractions, along with concurrent capecitabine, in cases where surgery cannot be guaranteed [21].

We believe that this approach would address the high risk of micrometastatic disease and subsequent development of distant metastases. The following would also reduce over-treatment of patients who will eventually develop distant disease, since those patients would only benefit minimally from the addition of chemoradiation and yet might develop additional toxicities.

Proton and Carbon Ion Therapy

Proton therapy is based on the use of proton beam radiation to deliver high doses of radiation to the tumor. Since protons are charged particles, they can have higher linear energy transfer and deliver higher relative biological effectiveness when compared to proton therapy, even under the same dosage and fractionation [22]. Furthermore, the main advantage of proton therapy lies in its ability to deliver the radiation dose in the beam path with minimal or no exit dose [23]. This unique feature of proton therapy enables proper dosing to the tumors while minimizing radiation side effects to normal tissue beyond the target. Moreover, by minimizing toxicity to normal tissues, proton therapy gives potential for dose escalation, which might help improve local control. In that regard, Thompson et al. performed a dosimetry study on 13 patients with unresectable cancer of the head of the pancreas [24]. The study compared IMRT and proton therapy plans and showed that within the low dose regions, proton plans had significantly less dose scatter to organs-at-risk like the duodenum, stomach, or small bowel. However, the results show higher doses to those structures in the intermediate to high dose regions [24].

Furthermore, some clinical data also favors the use of proton therapy. Terashima et al. performed a phase I/II trial to assess the efficacy and safety of proton therapy in locally advanced pancreatic cancer [25]. Patients received 50 Gy/25 fractions, 67.5 Gy/25 fractions, or 70.2 Gy/26 fractions, with concurrent gemcitabine. The results of this trial show 1-year local progression, progression-free, and overall survival rates comparable to those from historical data (81.7%, 64.3%, and 76.8%, respectively). Additionally, proton therapy treatment was shown to be safe and well tolerated, with less than 10% grade 3 toxicities [25]. Patients were subsequently assessed by endoscopy, and around 49.4% had radiation-induced gastric or duodenal ulcers, but only 3% exhibited grade 3 or more ulcer toxicity [26]. Despite dose escalation, no GI hemorrhage or perforations were found post-treatment [26]. Another prospective study of 11 patients was published by Sachsman et al. in 2014 and showed that proton therapy with concomitant capecitabine was well tolerated with no grade 2 or higher gastrointestinal toxicities [27]. The results also show a median survival of 18.4 months and a 69% local-progression free rate at 2 years [27].

Carbon ion therapy is based on a novel radiation therapy technique that uses the delivery of charged particles [28]. The use of carbon ions has a few advantages over protons [29]. First, carbon ions tend to have less lateral scattering and hence may provide a better dose distribution. Furthermore, carbon therapy provides a higher relative biological effectiveness and less oxygen enhancement ratio [30]. The decreased oxygen enhancement ratio is often desired for the eradication of hypoxic, radioresistant tumors. As such,

carbon therapy might allow the treatment of cancers that have been resistant to conventional X-ray therapy [28].

Despite the potential benefits of carbon therapy, only a few centers around the world have such technology. While limited centers provide carbon ion therapy, a large study by a group in Japan presents valuable information on the use of carbon therapy [31]. The study included 353 patients with pancreatic cancer treated with carbon therapy. Patients with locally advanced pancreatic cancer were treated in two phases. The first phase consisted of radiation therapy with 43.2 Gy in 12 fractions with concurrent gemcitabine (400 mg/m^2). In the second phase, the gemcitabine dose was increased to 1000 mg/m^2, and radiation doses were increased in 5% increments. This regimen resulted in a 2-year local control rate of 58% and a 2-year overall survival of 54% [31]. Additionally, retrospective data from the Japan Carbon-Ion Radiation Oncology Study Group analyzed 72 patients with LAPC treated with carbon ion therapy [32]. The study showed a 1-year overall survival of 73%, along with a median overall survival of 21.5 months. Moreover, the study showed excellent local control rates at 1 and 2 years (84% and 76%, respectively). However, most patients included in this study had tumors in either body or tail of the pancreas (58%), and the following might present a selection bias and sway the results. Lastly, despite the improved clinical outcomes noted, around a quarter of the patients experienced severe grade 3 or 4 hematological toxicities [32].

With more potential promising results from carbon therapy, the CIPHER phase III trial is currently comparing the use of IMRT to carbon ion therapy in patients with locally advanced, unresectable pancreatic cancer (NCT03536182) [33].

Stereotactic Body Radiation Therapy (SBRT)

SBRT is an advanced modality in radiation therapy that delivers highly conformal radiation with higher doses per fraction. SBRT is also delivered in fewer fractions (typically 1–5 fractions) and smaller target volumes when compared to more traditional radiation modalities. The conformity of SBRT planning allows higher radiation doses because of the steep dose decline at the edge of the target.

The initial use of SBRT in pancreatic cancer was a phase I dose escalation study using CyberKnife technology, where 15 LAPC patients were treated with single fraction of 15, 20, or 25 Gy SBRT [34]. Single fraction SBRT treatment was well tolerated, and no patients developed grade 3 or higher gastrointestinal toxicity. Patients had excellent local control rate and dose-limiting toxicity was not reached, even at 25 Gyx1 [34]. A subsequent phase II study from the same group at Stanford showed similar results, where patients treated with single fraction 25 Gy SBRT with sequential gemcitabine had an overall mean survival of 11.8 months, a 1-year overall survival of 50%, a 2-year overall survival of 20%, and a 94% local progression-free disease at 1 year [35]. Similar to the study by Koong et al., no patients developed acute grade 3 or more toxicity, and only 1 patient developed long term grade 4 duodenal perforations [34, 35]. These excellent results were extended with fractionated SBRT by Mahadevan et al. who reported outcomes on 39 LAPC patients who received 3 fractions of SBRT using Cyberknife. These patients exhibited excellent local control at 21 months (85%), with a median OS of 20 months and a median DFS of 15 months [36]. Late grade 3 toxicities were observed in less than 10% of patients [36]. Pollom et al. performed a single-center retrospective analysis comparing outcomes and toxicities in unresectable pancreatic adenocarcinoma patients receiving either single or five fractions SBRT [37]. Results showed that multi-fraction SBRT was associated with less toxicity, without compromising local control and survival rates [37].

More recently, Herman et al. performed a multi-center phase II trial investigating fractionated SBRT (33 Gy/5 fractions) with gemcitabine and showed a 1-year OS of 59% and a

1-year local progression-free disease of 78% [38]. The patients also tolerated treatment well, with minimal toxicities (acute grade 2 or more GI toxicities: 2%; late grade 2 or more GI toxicities: 11%) [38]. Moreover, another phase II trial by Comito et al. was published in 2017 and showed that LAPC patients receiving SBRT with 45 Gy in 6 fractions achieved excellent local control (90% local-progression free at 2 years) and had a median OS of approximately 19 months [39]. No patient developed acute or late grade 3 toxicity [39].

Currently, trials are investigating the use of intestinal radioprotection in SBRT to allow for further dose escalation and better local control and survival rates while maintaining low toxicities (NCT03340974) [40].

Magnetic Resonance Linac-Based Treatment

Linac (linear accelerator) treatment is a modern approach to radiation therapy that allows real-time monitoring of the tumor motion using magnetic resonance (MR) imaging for the subsequent image-guided plan adaptations strategies to precisely treat the target of interest [41]. The MR-linac is a hybrid linear accelerator combined with a magnetic resonance imaging scanner [42]. This set-up enables ideal real-time tumor visualization, despite the organ shifts secondary to respiratory motions. A comparative study of 4DCT and MR guided radiation therapy demonstrated favorable outcomes with MR real-time monitoring when dealing with tumors susceptible to respiratory motion [43]. Typically in an MR-Linac, flattering filter free beams are used to minimize the treatment time [44]. Currently, the linac energy in an MR-Linac is limited to 7 MV [44].

Because of the complex anatomical environment of the pancreas, surrounded by COR (critical organs-at-risk), the extensive tumor displacement synchronized with the respiratory motion, and the need for increased radiation dosing to the tumor site while maintaining minimal collateral damage to the surrounding normal structures, pancreatic cancer is considered an ideal candidate for MR-linac treatment [45]. Retrospective analysis of 44 inoperable pancreatic cancer patients treated with MR guided radiation therapy showed improved overall survival compared to historical data, with a 2-year OS of 49% for patients treated with high dose radiation [46]. Furthermore, no GI toxicity of grades 3 or more was noted in those patients [46]. Currently more trials are evaluating the role of MR guided radiation therapy in locally advanced pancreatic cancer (NCT03621644) [47].

Treatment Planning Procedures

In this section, we present all treatment planning procedures used for locally advanced pancreatic cancer patients at the University of Texas MD Anderson Cancer Center.

Pre-simulation Instructions

Patients are instructed to fast for a minimum of 3 h prior to planning simulation to ensure reproducibility in tumor localization, which is largely dependent on the stomach position and filling. Similar instructions will be given during the treatment to ensure the reproducibility of the patient set-up and the tumor localization.

Specific documentation pertaining to the allergies, especially to iodine contrast, is provided to every patient prior to the simulation. Any patients with iodine contrast allergy should not be given intravenous (IV) iodine contrast during simulation.

For patients that will receive IV contrast, a recent renal function test should be obtained to ensure adequate renal function and minimize the risk of contrast-induced nephropathy. Renal function tests within 2 weeks prior to simulation are accepted.

Patients that will receive SBRT treatment undergo endoscopy assessment prior to their treatment. The endoscopy helps tailor management into two parts. First, it allows the visualization of

the tumor to exclude invasion of the duodenum, which would preclude patients from receiving SBRT treatment due to the increased risk of toxicity [38, 48]. Second, around three or more fiducial markers are placed during endoscopy within 1 cm from the tumor or directly in the tumor if possible. Later on, fiducials are contoured in a cranio-caudal order on the appropriate respiratory phases and expanded by 3 mm. Fiducial markers check (with kV, cone-beam CT, or fluoroscopic imaging) are used in combination with daily CT imaging to ensure tumor position matching. The following steps are in line with the ALLIANCE protocol [49]. Daily image verification prior to radiation delivery is crucial, and we recommend postponing treatment, or even re-simulation when tumor position matching is not ideal. A common issue with tumor position matching is when gas or the position of the bowels is problematic. In such cases, treatment should be postponed, and patients should be preferably treated with anti-gas medication (simethicone) [18].

Patient Set-Up

Patients are positioned supine with both arms up and immobilized with upper Vac-Lock (Civco Radiotherapy, Orange City, Iowa). For patients receiving photon treatment, a wingboard and Medtec leg holder are used, while patients receiving proton treatment use a knee wedge for comfort and treatment reproducibility.

The Varian real-time patient monitoring (RPM) system is used to track patients' respiration patterns. The RPM box with two infrared reflectors is taped to the patient's abdomen at the midline between the xiphoid process and the umbilicus, and the RMP Infrared camera is adjusted to acquire the reflections from both reflectors in the RPM box and the acquired signal is interfaced to a computer for further processing using Varian RPM software. The monitored RPM motion is used as a surrogate for the patient's respiratory motion. RPM monitoring is not used in conventional fractionated treatment, and free-breathing scans are used instead. In some situations, respiratory gating can be used to monitor and manage respiratory motion [50]. In cases where patients cannot properly hold their breath, but can maintain a regular breathing pattern, patients can be treated with end expiratory gating in combination with fiducial matching [51].

Image Acquisition

After ensuring that the patient is comfortably positioned, an initial CT scan (scout scan) with slice thickness ranging from 2 to 3 mm is performed to assess the scanning range. Usually, this would extend from the carina to the iliac crests. Image acquisition techniques differ between patients capable of taking a breath-hold and those who cannot. If a patient is not capable to perform a breath-hold, a 4D-CT is performed instead. In patients capable of taking breath-holds, a few steps are followed to ensure adequate image acquisition. The following steps are as follows:

1. Perform an initial scout CT scan.
2. Determine the scanning range (usually from the carina to the iliac crests).
3. Perform free-breathing scan without contrast.
4. Provide clear instructions on inspiration breath-hold. Ideally, breath-holds should be comfortable and reproducible. Deep inspiration holds are not advisable, as those are challenging to reproduce during treatment.
5. Once the patient can perform proper and comfortable breath-holds, the breath-hold level is set in the RPM computer. The bars should be set as narrow as possible.
6. Perform practice runs with the patient to ensure comfort, consistency, and reproducibility of breath-hold.
7. Perform one or two CT scans without contrast while the patient is in breath-hold.
8. Perform a breath-hold CT scan with contrast. Contrast used is 150 mL of iodine contrast (Optiray 320) at a constant infusion rate of 5 mL/s. The first scan is performed at 30 s

after IV injection start. Up to 4 scans are subsequently performed at 30 s intervals.

9. The physicians will then select the best scan to visualize the tumor for treatment planning. Also, analyzing the movement of the target between various breath-hold scans gives an idea about the patient's compliance and the slight variations that occur despite breath-hold use. Those variations in target location should be accounted for as an internal target volume (ITV).
10. Finally, all CT scans are exported to the treatment planning system.

Treatment Planning

Treatment planning differs depending on which radiation modality is being used, and on whether a breath-hold will be performed or not. In this section, we present common treatment planning employed at the MD Anderson Cancer Center.

Conventional Dose/Fractionation, Non-SBRT, No Breath-Hold:

- Gross tumor volume (GTV) is contoured for the primary tumor (GTVp) and pathological nodes (GTVn).
- The following anatomical structures are also contoured:
  - Celiac artery
  - Superior mesenteric artery (SMA)
  - Porta hepatis
  - Duodenum (through the fourth portion)
  - Small bowel (mainly the jejunum near the ligament of Treitz)
- Once those structures are contoured, the clinical target volume (CTV) and planning target volume (PTV) can be obtained:
  - CTV = (GTV + celiac artery + SMA + porta hepatis) + 2 cm superior and inferior margin +1 cm radial margin
  - PTV = CTV + institutional set-up error (typically 0.5 cm margin)
- This regimen consists of delivering 50.4 Gy over 28 fractions (1.8 Gy/fraction). Radiation therapy is performed 5 days per week over 5.5 weeks and is usually delivered with concurrent chemotherapy.
- Figure 10.1 presents the contouring atlas for conventional dose/fractionation radiation therapy.

Non-SBRT Dose Escalation, with Breath-Hold:

- The GTV is contoured for the primary tumor only (nodes are excluded from high dose treatment volumes).
- Internal target volume (I-GTV) = GTV expanded to encompass all GTV positions seen on different breath-hold scans to account for target position variation.
- No CTV is generated here.
- Organs-at-risk are contoured, and a planning organ at risk volume (PRV) is created for the stomach, duodenum, and small bowel by adding a 3 mm margin to these organs.
- The PTV receiving high dose radiation can now be obtained:
  - PTV = ITV + institutional set-up error (typically 0.5 cm) – PRV
- In cases where the PTV extends into the PRV, a lower acceptable dose to the organs-at-risk is used.
- Usual dose/fractionation regimens include 60 Gy in 15 fractions, 67.5 Gy in 15 fractions, and 70 Gy in 28 fractions.
- Figure 10.2 presents the contouring atlas for dose-escalated non-SBRT regimens.

SBRT Technique:

For SBRT treatment, we follow the adopted treatment regimen discussed in the ALLIANCE study [49]:

- The GTV is contoured for the primary tumor only (nodes are excluded from SBRT).

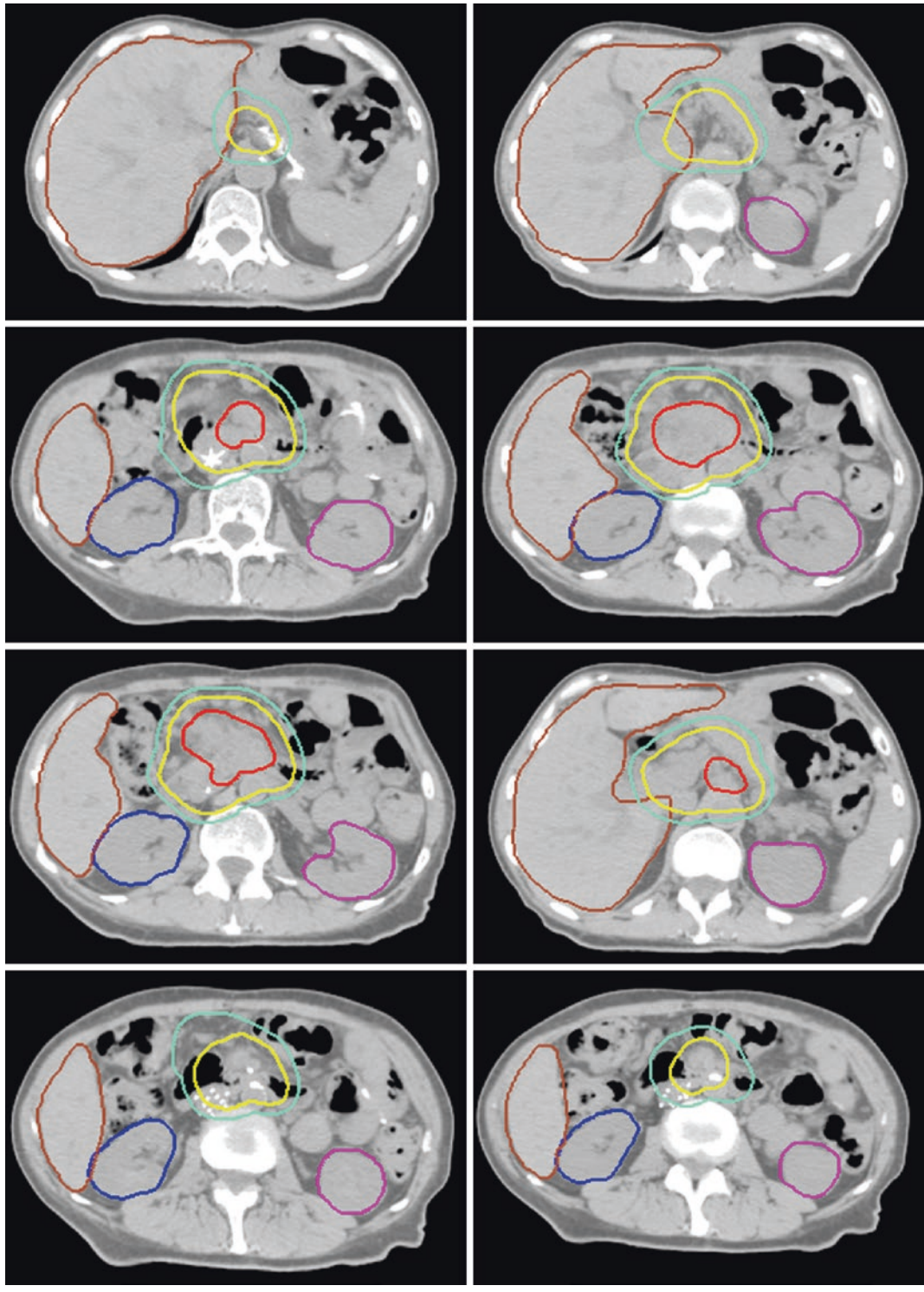


Fig. 10.1 Contouring atlas for conventional dose/fractionation radiation therapy (50.4 Gy/28 fractions). Target volumes: red—GTV, yellow—CTV, cyan—PTV. Organs-at-risk: brown—liver, blue—right kidney, purple—left kidney

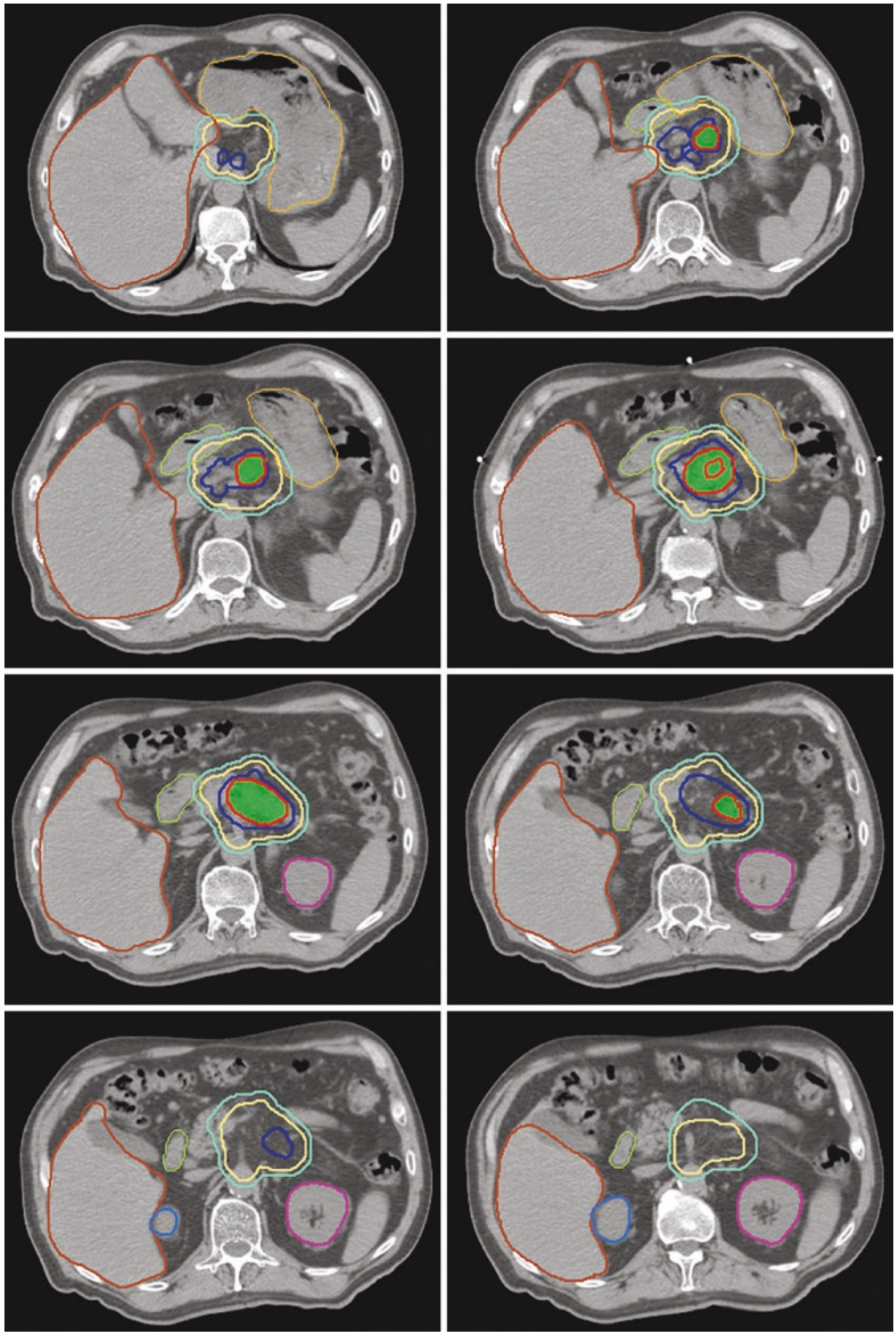


Fig. 10.2 Contouring atlas for dose-escalated, non-SBRT regimens. Target volumes: red—GTV, khaki—CTV, dark blue—PTV 60 Gy, green filled—PTV 67.5 Gy. Organs-at-risk: brown—liver, light blue—right kidney, purple—left kidney, light orange—stomach, yellow green—duodenum

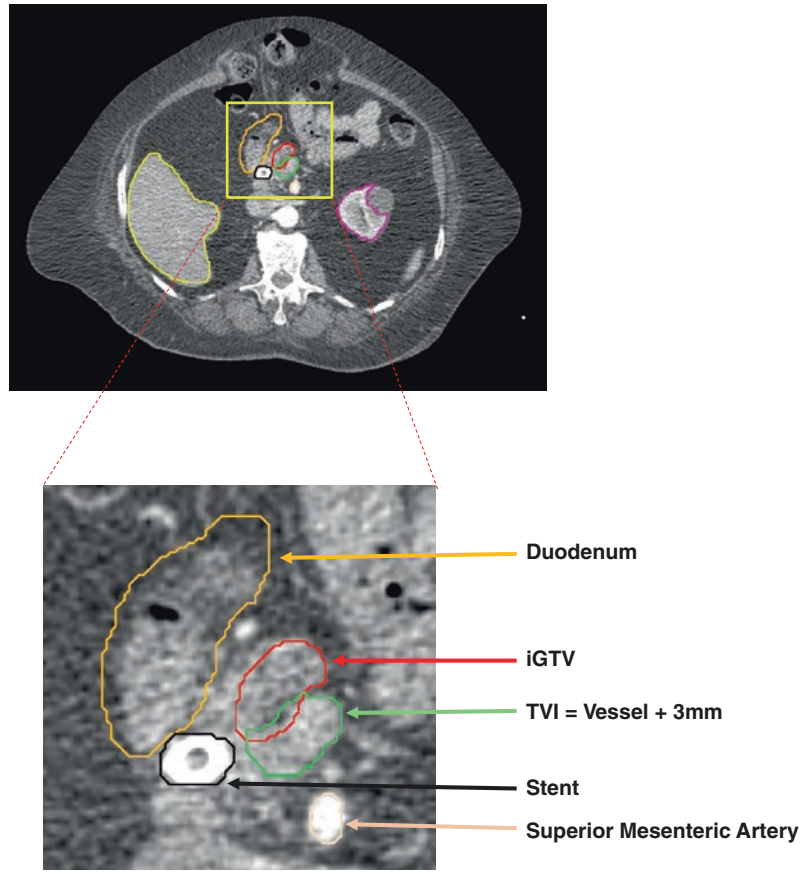


Fig. 10.3 Representative CT scan illustrating the iGTV and tumor vessel interface

- I-GTV = GTV expanded to encompass all GTV positions seen on different breath-hold scans to account for target position variation.
- No CTV is generated here.
- A tumor vessel interface (TVI) is contoured separately for each vessel that is in contact with the tumor (Fig. 10.3) including the following vessels:
  - Portal vein
  - SMA
  - Common hepatic artery
  - Celiac artery
- An internal TVI (I-TVI) is generated by expanding the TVI to account for all TVIs seen on different breath-hold scans.
- Organs-at-risk are contoured, and a PRV is created for the stomach, duodenum, and small bowel by adding a 3 mm margin to these organs. When possible, an ITV should be generated from either a 4D CT scan or multiple breath-hold scans. The duodenal and jejunal contours should be adherent to the anatomy seen on CT scanning and not a "bowel bag."
- Three different PTVs are then generated depending on the radiation dose used (Fig. 10.4):
  - For 25 Gy/5 fractions: PTV1 = (I-GTV + I-TVI) + 3 mm
  - For 33 Gy/5 fractions: PTV2 = [(I-GTV + I-TVI) + 3 mm] − PRV
  - For 36 Gy/5 fractions: PTV3 = (I-TVI + 3 mm) − PRV
- Figure 10.5 presents the contouring atlas for SBRT treatment.

Organs-at-Risk:

The following organs should be taken into consideration and contoured as organs-at-risk in the treatment planning:

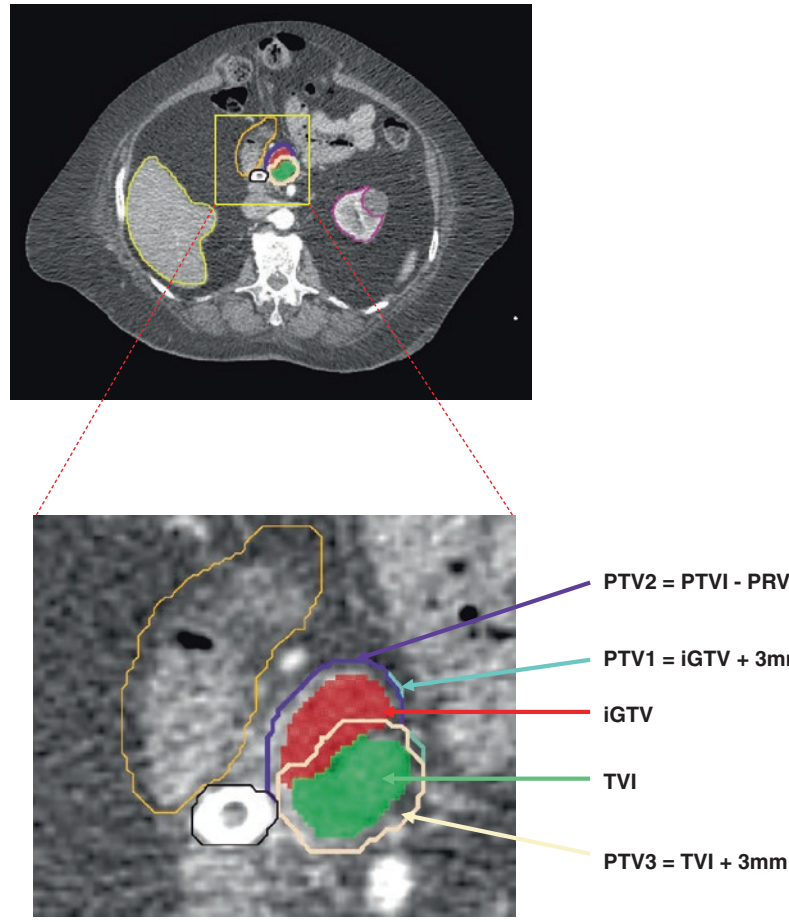


Fig. 10.4 Representative illustration of three different PTV margins

- Duodenum
- Stomach
- Bowel bag (for conventional dose/fractionation treatment)
- Small bowel loops (for dose escalation or SBRT). It is important to account for the jejunum near the ligament of Treitz
- Large bowel loops (for dose escalation or SBRT)
- Liver
- Right and left kidneys
- Spinal cord
- Spleen
- Lungs
- Heart

Planning Aims and Dose Constraints

Planning aims and dose constraints also vary depending on treatment modality.

Conventional Dose/Fractionation:

Target coverage aims:

- PTV1: 50.4 Gy, V100% > 95%, V95% > 99%, V105% < 10%, D_{max} < 120%

Dose constraints:

Table 10.1 summarizes the main dose constraints for conventional radiation treatment.

Dose Escalation (67.5 Gy/15 fractions):

Target coverage aims:

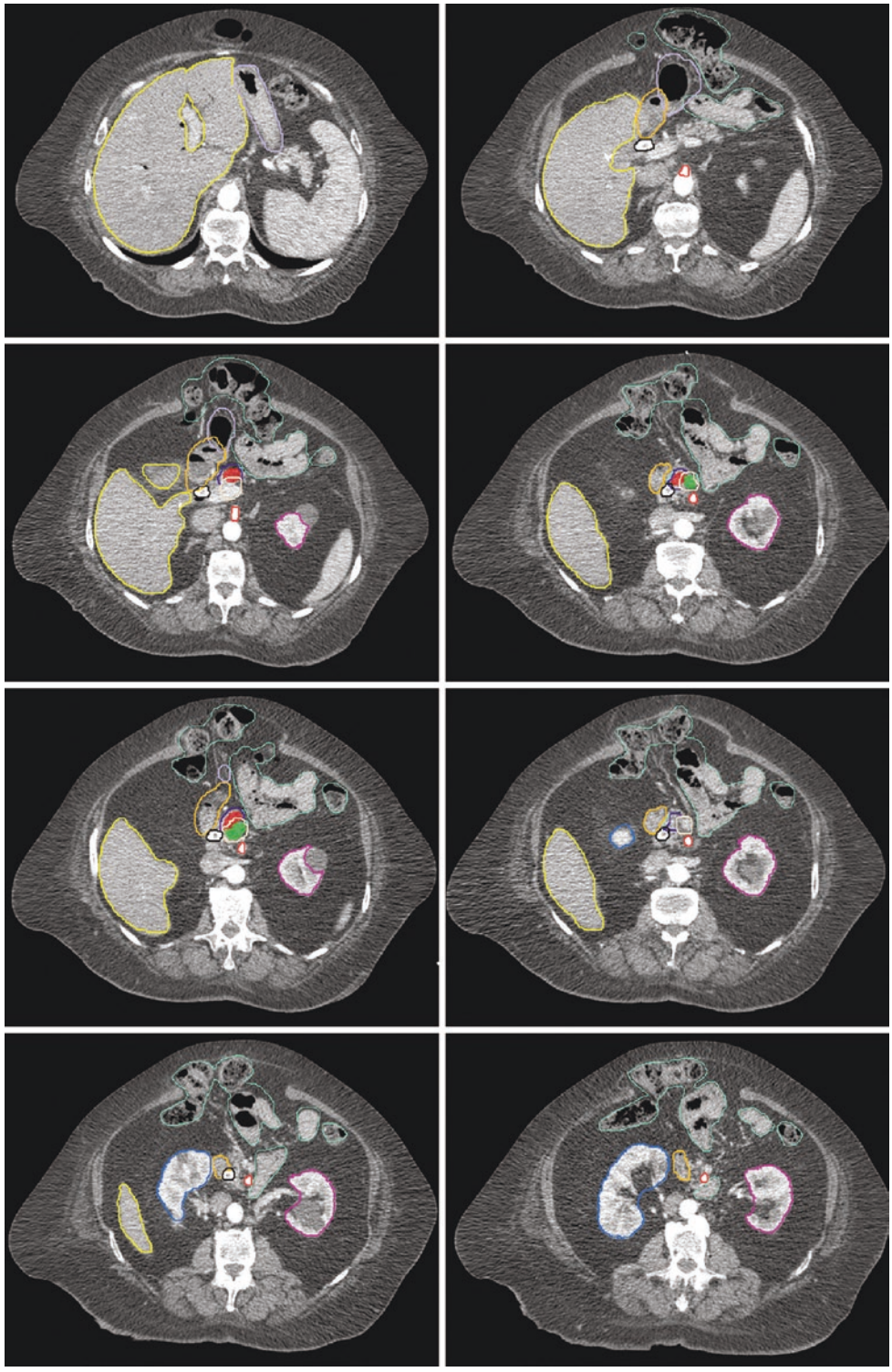


Fig. 10.5 Contouring atlas for SBRT. Target volumes: Red colorwash—GTV, Green colorwash—TVI, Cyan—PTV1 (25 Gy), SlateBlue—PTV2 (33 Gy), Tan—PTV3 (36–40 Gy). Organs at risk: Yellow—liver, Orange—duodenum, Purple—Left kidney, Light blue—Right kidney, Aquamarine—Small bowel, Lavender—Stomach, Steel Blue—Celiac, Tomato red—Superior mesenteric artery

Table 10.1 Organs-at-risk and dose constraints in conventional radiation treatment

Organs-at-risk	Constraints
Small bowel	D_{max} < 50 Gy
Liver	Mean < 32 Gy, V20 < 60%, V30 < 33%
Combined kidneys	Mean < 18 Gy; V20 < 33% for each; if one exceeds, spare the other with V20 < 20%
Spinal cord	D_{max} < 45 Gy
Spleen	Mean < 8 Gy

Table 10.2 Organs-at-risk and dose constraints in dose escalation radiation treatment

Organs-at-risk	Constraints
Small bowel	D_{max} < 40 Gy
Stomach Duodenum	D_{max} < 45 Gy
Liver	Mean < 24 Gy
Common bile duct	D_{max} < 60 Gy
Combined kidneys	Mean < 18 Gy; V20 < 33% for each; if one exceeds, spare the other with V20 < 20%
Spinal cord	D_{max} < 30 Gy
Large bowel	D_{max} < 50 Gy
Spleen	Mean < 6 Gy

- For each PTV: V100% > 95%, V95% > 99%, V105% < 10%, D_{max} < 120%

In dose escalation treatment, it is crucial to prioritize treatment safety. As such, meeting dose constraints is the first priority. Then, optimizing PTV and GTV coverage are taken into consideration.

Dose constraints:

Table 10.2 summarizes the main dose constraints for dose escalation radiation treatment.

SBRT Technique:

Target coverage aims:

- PTV1: 25 Gy, QQQD_{min} > 22.5 Gy
- PTV2: 33 Gy, D_{min} > 29.7 Gy
- PTV3: 36 Gy, D_{min} > 32.4 Gy, D_{max} 40 Gy

Table 10.3 Organs-at-risk and dose constraints in SBRT treatment

Organs-at-risk	Constraints
Duodenum	V20 < 20 cc
	V35 < 1 cc
Small bowel (other)	V20 < 20 cc
	V35 < 1 cc
Stomach	V20 < 20 cc
	V35 < 1 cc
Liver	V12 < 50%
Combined kidneys	V12 < 25%
Spinal cord	V20 < 1 cc
Spleen	No constraint

If the dose constraints cannot be met with the above target coverage, PTV1 will be reduced to 25 Gy/5 fractions with the aim that more than 90% of the PTV1 should be covered by at least 95% of prescription dose and D_{max} remains less than 110% of prescribed dose.

Dose constraints:

Table 10.3 summarizes the main dose constraints for SBRT treatment.

Treatment Verification

For patients treated using conventional fractionation, daily kV-IGRT is used for treatment position verification.

For dose-escalated regimens and SBRT, patients are imaged daily using CT-on-rails. The use of CT-on-rails provides diagnostic on-board CT imaging which allows soft tissue to soft tissue matching with high accuracy. This modality also allows dose escalation regimens to be delivered safely.

The following presents the different steps used in CT-on-rails at the MD Anderson Cancer Center:

1. The patient is brought into the treatment suite and positioned on the treatment table with the head towards the gantry.

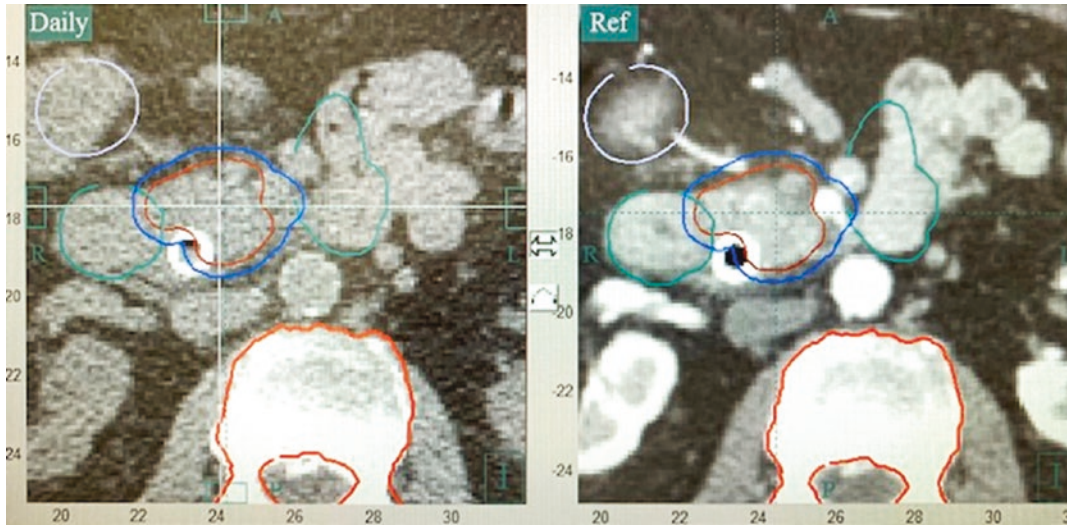


Fig. 10.6 Comparison between a CT-on-rails obtained daily and an initial CT scan obtained at simulation day. Maroon line—iGTV; Blue line—PTV, Red line- Vertebral body, Lavender—Jejunum, Teal—Small bowel

2. Once set-up has been established, the couch is rotated so that patient's head is towards the CT-on-rails.
3. The patient is imaged with CT-on-rails and the images are reviewed by either the treating physician or trained therapist.
4. The CT-on-rails images are compared to the planned CT images and contours (typically GTV). Isodose lines are also displayed on both sets of images (Fig. 10.6).
5. The CT-on-rails images are aligned with the planned images. Any required couch shift and position change are documented.
6. The couch is then rotated back so that patient's head is towards the gantry again.
7. After ensuring all previous steps, treatment can be initiated.

Table 10.4 summarizes the main radiation treatment modalities, and Figure 10.7 presents the treatment algorithm followed for patients with locally advanced pancreatic cancer

1. *Level of evidence is appropriate*: Consistent Level I and/or well-designed Level II evidence.
2. *Level of evidence may be appropriate*: Levels II and/or III evidence.

Level I: Evidence obtained from at least one properly designed trial.

Level II: Evidence obtained from well-designed controlled trials without randomization *or* evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center *or* research group or compelling results from uncontrolled trials.

Level III: Systematic review of case-controlled studies or individual case-control studies.

Summary

Patients with locally advanced pancreatic cancer have a poor prognosis. Those tumors are unresectable, and an ideal treatment with chemotherapy and radiation therapy has not been established yet. Thus, an early discussion with the patient in regard to treatment goals, along with early palliate referral is essential. While chemotherapy is

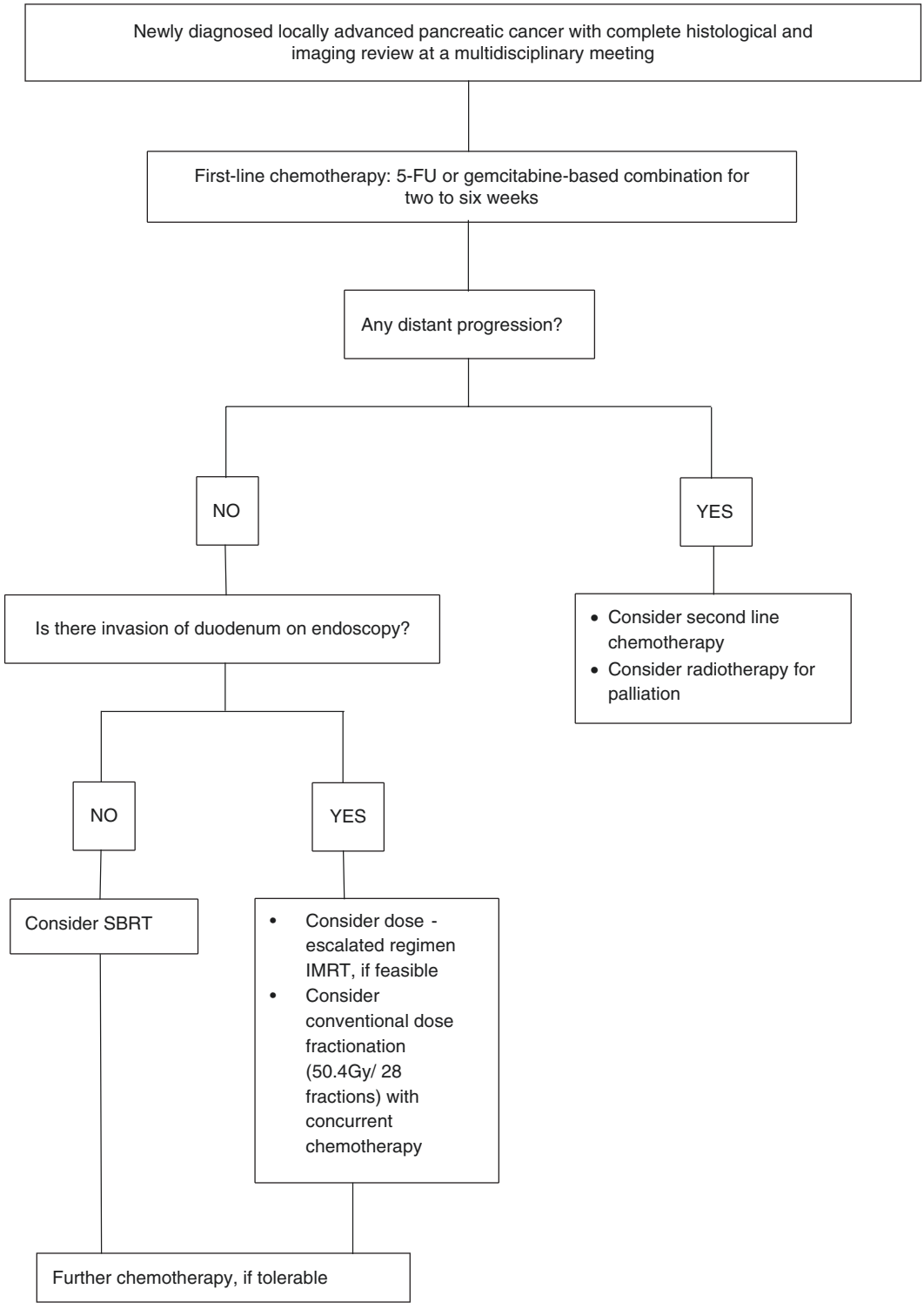
Table 10.4 Summary of different radiation therapy treatment modalities in pancreatic cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy	Level of evidence
3D CRT[a]	Definitive or consolidative therapy after chemotherapy	50.4 Gy 1.8 Gy per fraction 5 days/week	3 or 4 fields (APPA; right and left lateral)	Before radiation, and/or concurrent, and/or following radiation	1
IMRT VMAT[a]	Definitive or consolidative therapy before/after chemotherapy (IMRT/VMAT > 3D CRT if available)	50.4 Gy 1.8 Gy per fraction 5 days/week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Before radiation, and/or concurrent, and/or following radiation	1
SBRT	Consolidative therapy after chemotherapy	33 Gy; 6.6 Gy per fraction (or 25 Gy; 5 Gy per fraction if dose constraints are not met with 33 Gy) Delivered over 5 days	Linac-based: IMRT with multiple coplanar isocentric beams Cyberknife: Multiple noncoplanar nonisocentric beams	Before radiation, and/or following radiation	2
Proton therapy[b]	Definitive or consolidative therapy before/after chemotherapy	50.4 Gy 1.8 Gy per fraction 5 days/week	Typically, 3 fields (posterior oblique: Right lateral oblique) with a 3:1 weighting to the posterior field to limit spinal cord dose	Before radiation, and/or concurrent, and/or following radiation	2

[a]High-energy photons (≥10 MV) preferred as lower energy may result in more gastrointestinal toxicity
[b]Treatment energy is determined depending on depth of target volume

used to try and prevent distant progression, radiation therapy aids in achieving local control which has been associated with a survival benefit in some studies.

Different radiation regimens can be considered, and no standard treatment has been established yet. We advise that the modality choice be dependent on the availability of equipment, the dose and fractionation of treatment, as well as the dose received by normal tissue. IMRT, VMAT, and proton therapy can be used in LAPC and tend to have improved dose distribution to the target volumes while minimizing the radiation dose to normal tissues. SBRT can also be considered in LAPC patients in cases where the tumor does not invade the duodenum. Because of the high doses delivered by SBRT, proper respiratory and tumor motion management should be implemented to reduce collateral radiation dosing.



*IMRT, VMAT, and SBRT are commonly used modalities in the LAPC setting; 3D CRT and proton therapy may be considered as options

Fig. 10.7 Treatment algorithm for locally advanced pancreatic cancer

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Part III

Management of Resectable and Borderline Resectable Disease

11 Management of Resectable and Borderline Resectable Disease: Surgery

Ching-Wei D. Tzeng

Introduction

While the 5-year overall survival of patients with pancreatic adenocarcinoma (PDAC) remains a dismal 10%, those with localized disease have benefited from the combination of more effective doublet/triplet chemotherapy regimens and continued improvements in surgical techniques and outcomes, in the past decade. Almost 2 decades ago, CONKO-001 proved that surgery alone is insufficient treatment for localized PDAC, and thus no further surgery alone trials can be ethically allowed [1]. With modern surgery and chemotherapy, reported median overall survival (OS) durations have increased from traditionally 18–24 months to 43–54 months in well-selected contemporary patients [2, 3]. While multimodality therapy (systemic therapy with surgery) is the standard of care for PDAC, surgery remains the most critical component. Without surgery, long-term survival, even for patients with anatomically and borderline resectable (AR and BR) disease is close to 0%. In this chapter, the two major operations for right sided and left sided pancreatectomy will be reviewed as will preoperative, intraoperative, and postoperative considerations.

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History of Pancreatoduodenectomy

While the pancreatoduodenectomy (PD), or "Whipple" procedure, has been around since 1935, it was John Cameron who revolutionized it in the USA and made it a mainstream operation [4, 5]. Through a diaspora of his trainees and his teachings from Johns Hopkins, the PD has become a routine operation for cancer surgeons. However, the basis of modern safe surgery took more than 4 decades of iterative learning to build up, as Dr. Cameron reported. There are still improvements to be made, especially in reducing the risk of the central problem of PDs—the risk of postoperative pancreatic fistula (POPF), the Achilles heel of the operation and its primary cause of subsequent cascade of complications that leads to significant morbidity and even mortality [6]. In an era in which no patient expects to die from the actual operation, PD mortality remains 7–10% even in USA and Western European countries [7, 8], especially when you take into account 30–90-day outcomes, not just inpatient outcomes. The lack of regionalization and centralization of procedures is perhaps insurmountable in the US healthcare system, unlike that of other countries [9–11]. There is a plethora of data which point to the worse operative and oncologic outcomes when patients are not treated at major academic centers.

The Pancreatic Surgery Service Line at MD Anderson Cancer Center has advocated a stan-

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_11

dardized approach to the PD with resection occurring in a clockwise fashion and the reconstruction in a counter-clockwise direction [12]. With the six steps of resection and three steps of reconstruction, it is easy to replicate the operation each time and to communicate with trainees and OR staff about the exact progress of the operation. There is still a lot to be done in ensuring that the PD is standardized enough in the USA to reduce complications including POPF and death, which arguably would improve OS for all surgical patients more than any particular new cytotoxic therapy.

Preoperative Management

Preoperative Period: Opportunity for Optimization

The putative reasons for considering neoadjuvant therapy include treating micro-metastatic disease, downsizing the primary tumor anatomy, testing the tumor biology, and optimizing the patient condition. Despite concerns that patients may demand surgery upfront, with proper counseling, patients almost universally understand and agree with the concept of using preoperative therapy in a disease like PDAC where almost all patients have micro-metastatic disease at presentation regardless of how localized the tumor may seem [13]. With proper care, there is no increased surgical morbidity in patients treated with a neoadjuvant approach [14].

Endoscopic biliary stents are exchanged from plastic to metal to prevent cholangitis episodes [15]. Prehabilitation programs are routinely set up regardless of your baseline age or performance status [16, 17]. Geriatrics evaluations are added if needed to test cognitive function and ensure medical optimization for surgery in the next few months. Nutrition counseling is mandatory to either build muscle mass in cachectic patients or lose excess fat in those who are obese [18, 19]. All of these services are bundled as soon as the patient meets the surgeon for the first time.

Decision for Surgery

For all patients with AR and BR tumors, we use the internationally recognized MD Anderson clinical classifications which use the A-B-C system to stratify anatomy, biology, and condition, for localized PDAC [20, 21]. While surgeons commonly focus on tumor anatomy at presentation, we argue that condition supersedes all, and biology supersedes anatomy. As mentioned above, borderline type C patients are those with reversible comorbidities (deconditioning, older age, cardiac issues, etc.) who have the opportunity for optimization during the neoadjuvant therapy period [22]. Their greatest risk postoperatively is failure to be rescued if we do not optimize the issues from disease presentation. Borderline type B patients present with suspicion of metastatic disease without obvious M1 disease. This can be enlarged regional nodes, indeterminate lesions in the lungs or liver, and most commonly an elevated CA19-9 above 500–1000 U/ml. Our experience is that less than half of borderline B patients get resection with many manifesting metastatic disease during the neoadjuvant period, which saves them from the unhelpful sequelae of a futile pancreatectomy [20]. Finally, borderline A is perhaps the most straightforward for a surgeon. These patients have no major comorbidities or tumor biology concerns. These patients need a safe operation that is well-planned and well performed with negative margins, patent venous reconstruction, leak-free pancreatic reconstruction, and return to baseline function within a few weeks. Our decision for surgery is thus framed around stability and/or improvements in each of these three categories: A-B-C- at each restaging visit [23, 24].

Carbohydrate antigen (CA) 19-9 is a useful tumor marker in about 80% of Americans. About 10% do not produce it. And another 10% have normal levels even at diagnosis, regardless of tumor burden. For the majority of patients, it can be used (once the bilirubin is <2.0 g/dL) as a baseline to compare future response to chemotherapy with the ideal goal of normalization to enter the best prognostic category [25]. In those

with rising CA19-9, staging laparoscopy (at separate time) from the planned pancreatectomy is a useful tool to obtain clarity on the tumor biology before consenting a patient for a potentially large operation. In those with normalized CA19-9, the yield of laparoscopy is quite low, and thus a separate laparoscopy from the date of surgery is not cost-effective [26].

Operative Steps

Pancreatoduodenectomy

The use of our MD Anderson Cancer Center named steps allows similar nomenclature among surgeons, trainees, and operating room staff, so that everyone knows what step is being performed within a long operation.

Step 1 starts with opening the lesser sac and separating the transverse mesocolon from the greater omentum. One simple purpose of this step is to identify the pancreas which can sometimes be buried underneath fat or fibrosis from tumor- or procedure-related pancreatitis. The anatomic purpose of this step is to find the middle colic vein to follow until its insertion into either the superior mesenteric vein (SMV) directly or into a gastrocolic trunk (combined with the gastroepiploic vein) before entering the SMV. The "tunnel" under the neck of the pancreas is usually just millimeters away. Many surgeons will ligate the middle colic vein or gastrocolic trunk at this step to avoid avulsing it during the rest of the transection, especially in cases where a vein resection will require its ligation anyway. The degree of exposure of the SMV is surgeon dependent. Some surgeons will go ahead and expose a good stretch of SMV up to the tunnel or below a known area of SMV encasement to ensure a proper landing zone caudally. If there is no vein resection (such as a typical AR case), then the full exposure of the SMV is not required at this point, because it can be done in rhythm during Step 6. Step 1 continues with separation of the right colon from the duodenum (as if performing a right hemicolectomy). A formal Cattell–Brasch maneuver is not necessary, but mobilization of the entire right colon does allow full view of the retroperitoneum and the turn of the duodenum for Step 2.

Step 2 is the Kocher maneuver. Historically, this was a step used to mobilize the head of the pancreas to expose the inferior vena cava (IVC) and to palpate the superior mesenteric artery (SMA) coming off the SMA. Surgeons would use this step as a "make or break" step to see if the SMA was involved. While we encourage a liberal Kocher maneuver to expose the IVC, left renal vein, aortocaval groove, and aorta, we do not encourage the inexact use of palpation of the SMA to confirm or deny resectability. Instead, the decision on SMA clearance and resectability (AR, BR, or LA) is made from pancreas protocol CT scans before the decision for surgery. Up to this point, no irreversible steps have been made.

Step 3 is the portal dissection. Removing the station 8a lymph node, known as the common hepatic artery (CHA) node, exposes the bare white adventitia of the CHA to follow to the proper hepatic artery (PHA). Following the CHA to the PHA, the surgeon will encounter the right gastric artery superficially, which is often diminutive in size and can be easily ligated. This starts the process of dissecting the hepatoduodenal ligament and creating some laxity in this space which is really only a few centimeters. Slowly clearing the fat and some veins in a horizontal direction between the PHA and the cystic duct, eventually the PHA with its bifurcation, common bile duct (CBD), and the cystic duct with gallbladder can be readily identified. If there is a gallbladder, the gallbladder can be resected at this point. Then attention is turned back to the CHA-PHA junction where the gastroduodenal artery (GDA) comes off. This should be carefully dissected, often by freeing up more laxity of the CHA and PHA first to ensure that the future base of the ligated GDA is not manipulated or damaged. Once a sufficient length of GDA stump is available, it can be doubly ligated and sutured before dividing. If there is limited length, focusing on the top side is adequate since the lower portion can be clamped and widely sutured into the specimen side. Once the GDA is divided, this releases the PHA to allow dissection of the station 12a and 12b nodes (often

flat and small) to show the portal vein (PV) underneath. Going then to the right side of the CBD, the station 12p nodes (portocaval nodes) can be taken downward toward the specimen to expose the PV from that side. Then the CBD can be isolated from the PV. This is a good time to reconfirm that there is no accessory or replaced right hepatic artery running posterolateral to the CBD before dividing the CBD. The CBD can be divided at or near the cystic duct junction or above it depending on tumor anatomy and surgeon preference. Any biliary stent should be accounted for and removed. Some surgeons will do a bile and stent culture in case there is a postoperative infection to direct antibiotics.

Step 4 is the division of the distal stomach or proximal duodenum, depending on classic PD vs. pylorus-preserving PD. Multiple studies have shown no oncologic difference in these techniques. However, there is continued debate on the impact on postoperative delayed gastric emptying (DGE) [27]. We tend to create a 2-staple line Hofmeister shelf to sew the eventual gastrojejunostomy to the lower shelf at a natural angle that facilitates gastric emptying.

Step 5 is the mobilization of the ligament of Treitz and division of the proximal jejunum about 10–15 cm from the ligament. There is no need for excessive waste of bowel length here. We tend to divide the jejunum at a point that can be loosely brought to the planned reconstruction, keeping in mind that the reach will be even easier at the end when a mesocolic window under the right colon is made in the typical bare space between the middle colic and ileocolic vessels.

Step 6 is the most important and longest step of the operation. At this time, the pancreatic neck tunnel is created carefully using instruments (never the surgeon's finger) between the SMV and PV under the neck. Sometimes, if there is tumor at the portal vein (PV)–superior mesenteric vein (SMV)–splenic vein junction, the planned transection line will need to be a tunnel over the splenic vein under the true pancreatic body for an "extended" PD. Once the pancreas is divided with cautery, the pancreatic duct can be identified at this point. If too small to see, often looking on the specimen side will offer a clue to the location on the remnant side. The SMV is then skeletonized on its anterior surface all the way to the turn of the duodenum. If not already, the gastrocolic trunk will be ligated and divided. The lower extent of the dissection starts at the first jejunal vein which is most commonly posterior. For tumors stuck to the SMV, this will need to be ligated. But for AR tumors, this can be saved, noting that there are usually several tiny veins draining the uncinate which should be carefully taken with energy device or ties. Once cleared, this is the lowest point of SMA dissection to start. For the SMA, there are two general philosophies of exposure. One can go from the right side "under the SMV" while pulling the SMV to the left or from the left side (straight down) while pulling the SMV to the right. The latter requires division of all colic drainage into the SMV to allow the SMV to be pulled right with vessel loops.

While for AR tumors, the SMV can just be cleared one tributary at a time to then expose the SMA underneath, an SMA-first technique is useful to learn for BR tumors that are abutting or attached to the PV-SMV. The author's personal preference is to do a right sided approach with dissection of the SMA base off the aorta first to clear its lymphatic tissue and to show the "target area" for dissection from the posterior jejunal vein area of the distal SMA. Going back to the distal SMA, the peri-adventitial tissue (lymphatic tissue and perineural tissue which wrap the artery like insulation of a household pipe) should be dissected until the bare white adventitia is seen. In thin patients, this can be just 1–2 mm. In obese patients and those with a lot of visceral fat, this dissection can be several mm of tissue that must be cleared. There are studies which show tumor cells penetrating past the uncinate to this tissue along the SMA [28]. That is why simple palpation and using an energy device or stapler along this peri-arterial tissue without seeing bare white adventitia are oncologically unsound. The J1 artery (first jejunal artery) is typically curling back under toward the proximal jejunal mesentery by definition. There is almost always an inferior artery to the uncinate here that should be ligated and divided to then free the J1. If there is a lower SMV-SMA tumor, then the J1 can be sacrificed (like the posterior jejunal vein if needed) without concern for blood supply. Once

cleared of the J1 artery and its branch to the uncinate, the surgeon can march along the bare SMA, clearing at least 180° but never 360°, looking for at least 1–2 additional pancreatic arteries, especially looking for one at the SMA base area. This completes the SMA-first approach (Figs. 11.1 and 11.2).

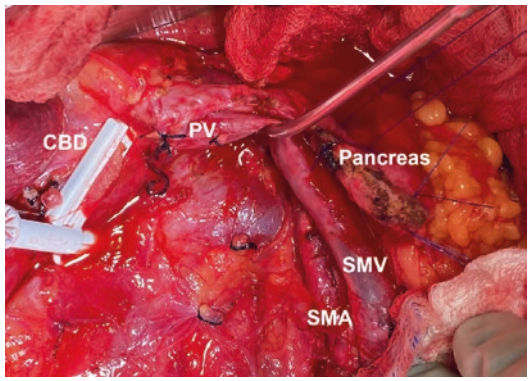

Fig. 11.1 Typical exposure of distal superior mesenteric artery (SMA) at level of J1 artery with the superior mesenteric vein (SMV) pulled to the left. Skeletonization should expose 180° of the SMA. Divided pancreas in background. Divided common bile duct (CBD) labeled

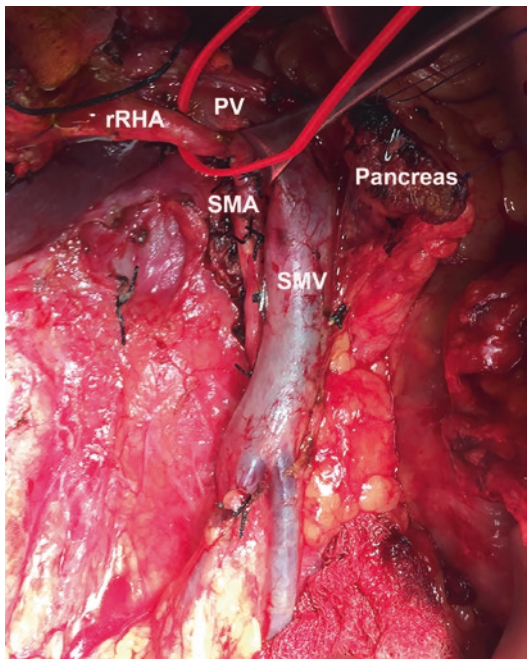

Fig. 11.2 Exposure of proximal SMA with takeoff of replaced right hepatic artery (rRHA). Superior mesenteric vein (SMV) and portal vein (PV) junction pulled to left. Note the complete skeletonization of the SMA with ties directly on pancreatic artery branches. No tissue is left on this side of the SMA

The remaining specimen is just hanging on the SMV-PV. The lymphatics along the upper specimen under the PV can be cleared with energy device or ties. Then all that is left is the actual pancreas (and tumor) on the SMV-PV. Here the surgeon can continue to clear one tributary at a time until the final area. If there is a final area of vein involvement, a decision should be made. The question is whether the tumor can be dissected off sharply with scissors in a desmoplastic plane (with or without vein clamping) or if a true vein resection is needed. If a true vein resection is needed, it will be a side repair, side patch, end-to-end, or interposition graft. If there is going to be potential narrowing, we discourage side repairs that could cause clotting by reducing flow. Side patches are rarely used as well. End-to-end repairs preserve laminar flow the best. Interposition grafts (preferentially using the internal jugular vein) are reserved for long distances of 5 cm or more. The SMV can be mobilized for end-to-end by loosening additional right colon (toward a true Cattell–Brasch) and taking down the falciform ligament to bring the liver (and PV) downward. Table 11.1 outlines pearls and pitfalls of these six steps.

Considerations for Vein Involvement

For a straightforward vein involvement situation, even for AR tumors, or BR tumors with significant downsizing to abutment without encasement, there is sometimes a need to clamp the vein with a side-biting clamp for the final detachment of the specimen from the SMV-PV. The side-biting clamp allows some flow to the liver for the anesthesiologist. Our group typically will circulate 50 units of heparin per kg intravenously for 3 cardiac cycles before vein manipulation or clamping. The paradox is that when working with the SMV-PV, postoperative thrombosis is much more morbid than the threat of intraoperative bleeding (if clamps are correctly placed). Scissors will often be sufficient to take the tumor off the vein for AR cases and a bit of true wall can be taken for BR cases. This can be repaired while clamped with no blood loss and minimal time constraints. For the repairs that will

Table 11.1 Key points of the 6-step pancreaticoduodenectomy

Steps	Key points	Pearls	Pitfalls
1	Entering lesser sac and colon mobilization	• Follow middle colic vein to SMV • Expose pancreatic head and duodenum	• Middle colic vein avulsion from SMV • SMV bleeding from aggressive dissection before full exposure
2	Kocher maneuver	• Exposing IVC, left renal vein, aortocaval groove • Expose until under the SMA	• Not exposing enough and thus requiring more work during Step 6
3	Portal dissection	• Follow CHA to find GDA • Palpate and check posterolateral to CBD for aberrant RHA	• Ligating GDA before ensuring PHA protected • Dividing CBD before ensuring aberrant RHA is protected
4	Stomach transection	• Setup eventual reconstruction angle when stapling	• Bleeding from stomach staple line
5	Jejunum transection	• Staple minimal length of jejunum	• Stapling too much jejunum
6	Pancreatic transection and retroperitoneal dissection	• Creating tunnel to left of PV under body when tumor is too close to neck • SMA dissection starts at the level of the posterior jejunal vein • Bare SMA adventitia should be exposed for 180°	• Blunt dissection in the tunnel • Poor SMA visualization leading to branch tear and SMA injury with urgent suturing • Tumor bleeding if all venous tributaries are ligated before SMA branches taken • Leaving tissue along SMA due to fear of SMA injury • Stapling or energy device along the uncinate while leaving gross tissue on SMA

need end-to-end repair, one clamp each will be needed above and below the landing zones (two clamps if SMV resection because you need one for the splenic vein and one for the PV), ideally at least 1 cm away since the vein retracts to the clamp faster and further than one realizes when cut. The tumor and vein can be taken off quickly and the vein reconstructed per surgeon preference running with air knot for "growth" or interrupted for alignment. For interposition grafts, the internal jugular (usually the left since many patients have their ports on the right side) can be taken by a typical incision along the sternocleidomastoid, harvesting the vein from the facial vein at the top and the insertion to the innominate vein below. With no valves, there is no concern about the direction of the graft. We typically sew the more difficult end of the graft first. This can be the portal side if we are quite high. This can be the SMV side if we are quite low into the mesentery. Either way, the concept is to not allow the clamped landing zones to slip from the clamps. After reconstruction, the heparin is not reversed. Patients remain just on prophylactic low molecular weight heparin per usual plus an 81 mg aspirin.

Margins for the pancreatic neck and CBD are usually sent and if positive, re-taken if technically and safely feasible. There is debate [29] about the oncologic value of this and thus we choose never to chase a microscopically positive margin into a total pancreatectomy, but if an additional 1 cm piece of pancreas can be safely mobilized off the splenic vein, avoiding the splenic artery, then we will often take this extra piece and send it for permanent section.

Reconstruction

Reconstruction Step 1 is the pancreaticojejunostomy. There is no international consensus on the ideal method. We typically recommend a 2-layer modified Blumgart technique in which a 3-0 polypropylene straightened needle is used to wrap the bowel around the cut end of the pancreas to sandwich it around the inner duct-to-mucosa reconstruction. The inner layer is created using 5-0 polydioxanone suture in an interrupted fashion to allow ideal alignment and reproducibility for training fellows.

Reconstruction Step 2 is the hepaticojejunostomy. Good blood supply at the tip of the cut CBD or common hepatic duct (depending on if the cut is below or above the cystic duct junction) is confirmed before a single layer 5-0 polydioxanone suture anastomosis is created about 10 cm distal to the pancreatic anastomosis. We then tuck the falciform flap between the pancreatic and biliary anastomoses to cover the GDA stump.

Reconstruction Step 3 is the gastrojejunostomy which is performed either with stapler or handsewn technique with a recent preference toward handsewn in our group due to our own DGE rates. Of note, the Pittsburgh group has used video analyses to suggest a large (4.5 cm), handsewn, angle anastomosis for ideal DGE mitigation [30]. Otherwise, there is no international consensus on this reconstruction [27].

Finally, we will not expound on the debate regarding surgical drain or no drain. As a group, our protocol does advocate a drain placement over the anastomoses. The drain amylase is measured on postoperative days 1 and 3, and depending on our cutoff levels (created based on our own patient population) we will remove them as early as possible, ideally by day 3 [31]. This follows the international consensus that if a surgeon does place a drain, it should be removed early by day 3 when possible [32, 33].

Distal Pancreatectomy

While distal pancreatectomy does not receive the attention of its right sided counterpart, the left sided pancreatectomy also requires a number of consistent operative steps to ensure a safe operation, negative margins, and adequate locoregional clearance. There are essentially two philosophies in dissection—medial to lateral or lateral to medial. While this can be surgeon preference for AR cases, BR tumor anatomy can dictate the steps to allow the vein resection to be done as the final step as with the PD with vein resection.

Gaining access to the lesser sac is similar to Step 1 of a PD. Exposure of the pancreas and spleen, including seeing the inferior border of the pancreas and the lower pole of the spleen helps define the boundaries of the resection. This is accomplished by taking down the splenic flexure and allowing gravity to relax the transverse mesocolon and left colon out of the pancreatic resection bed. The stomach is reflected upward to be retracted after using an energy device to separate the omentum from the splenic attachments (leaving some omentum on the specimen). Care should be taken to save as much of the gastroepiploic arcade until the short gastrics are reached. This saves collateral blood flow to the stomach. The short gastrics can be ligated easily with modern energy devices. This creates further space between what needs to be saved (stomach) and what will go (pancreatic tail and upper pole of spleen).

Sometimes due to tumor encasement, there is sinistral hypertension from the splenic vein being narrowed or occluded. To prevent splenic engorgement and potential for bleeding, the splenic artery can be tied off early in the operation. If the tumor is not at the neck the splenic artery can be ligated early. Often for neck and body tumors, access to this area is not readily available early in the case. In these cases, a simple tie or figure-8 ligation of the distal splenic artery past the tumor can reduce all flow to the spleen and start its decompression.

To find the splenic artery, the safest method is to start on the CHA as above with the PD. By removing the station 8a lymph node, the surgeon can then follow the CHA to its base and see the celiac trifurcation and the splenic artery base. Once an adequate splenic artery stump is dissected, double ligation can be accomplished as with the GDA in the PD.

At this point, if AR with no vein resection is needed, the tunnel can be dissected and the neck transected as with the PD. Transection can be via cautery or via stapler with the caveat that the stapler should not be used in neck tumors with close margins because the stapler (and its reinforcement) uses up several millimeters of margin. Then the splenic vein can be ligated or stapled right at its insertion to the PV. If there is narrowing right at the confluence, a side-biting clamp can be used here to cut the splenic vein and repair the side wall of the PV. The rest of the

dissection is then carried forth medial to lateral, taking the retroperitoneal tissue and the lymphatic tissue above the splenic artery as part of the locoregional clearance. For BR tumors, if may be easier to go lateral to medial and leave the last part attached to the PV-SMV (as with the PD with vein resection) so that safe clamping can be applied before vein resection and reconstruction.

For a pancreatic neck which was transected with cautery, we use direct suture ligation of a visible duct (6-0 polypropylene) when possible with pledget-reinforced U-stitches to tamponade the cut edge of the pancreas to reduce POPF risk. Despite no international consensus [34], drain placement is routine with postoperative days 1 and 3 drain amylases checked per our published recommendations, which we review annually with our entire pathway review [31].

Postoperative Management

Enhanced Recovery

The 2016 rollout of our Risk Stratified Pancreatectomy Clinical Pathways immediately reduced our postoperative length of stay (LOS) from 9 days (consistent with median LOS from national databases) down to 6 days [35]. This was due to using three separate pathways so that patients who could be fast tracked were no longer being held back in their dietary advancement and discharge planning with higher risk patients. We have continued iterative changes to reduce nasogastric tube usage, number of days of drain use, and total and discharge opioid volumes. At the time of this publication, further iterative updates have reduced median LOS for high-risk PD to 5 days and low-risk PD to 4 days without increasing readmission rates.

Quality Measures

The role of the surgeon cannot be understated when it comes to ensuring a quality outcome. While future metrics may involve more patient-centered outcomes such as return to baseline function and ability to return to intended oncologic therapy, for now, the only quality metrics are pathology based.

As with other gastrointestinal cancers such as colon and stomach, pancreatectomy has recommended lymph node harvest rates based on right side ($\geq$15) vs. left sided operations ($\geq$10) [36]. Obviously, nodal harvest rates do not tell the entire truth of how the operation went or whether the patient had any postoperative complications, but as with other cancers, it is used as a surrogate in large national datasets for doing a sufficient locoregional clearance around the primary tumor.

The SMA margin is sometimes called the retroperitoneal margin, and it is one of the 3 standardized margins that should be checked at minimum in a PD. [12] The other two are the pancreatic neck transection margin and the bile duct transection margin. Because of the putative danger of operating along the SMA, many surgeons will use palpation alone to find the SMA and use energy devices to seal the SMA periadventitial tissue or even staple or cut through uncinate tissue to avoid skeletonizing the SMA itself. As we note in our operative steps above, a dissection plane directly on the bare white adventitia will ensure the maximum cancer clearance and safely identify pancreatic branches to avoid injuring the SMA. As discussed in the ACS Operative Standards book and video series, the SMA margin should be routinely cleaned off the SMA and then should be standardly sectioned by pathology to note the actual distance from the cut surface [37].

Perhaps one of the most studied complications in surgery is the postoperative pancreatic fistula (POPF) which has caused so much morbidity and death for pancreatectomy patients for decades [38]. While risk scores have been created and validated, there still remains no perfect mitigation technique besides excellent surgical technique. Even a randomized trial showing the reduction of POPF from pasireotide has not been externally validated due to its original mixed cohort of high- and low-risk patients and definitions of POPF which were not consistent with international guidelines [39, 40]. Our group used

pasireotide for 2 years and abandoned it after internal analysis showed no changes in our outcomes and certainly no advantage in our low-risk "Green" pathway patients [41].

Complications such as blood transfusions and major complications may have sequelae beyond worse short-term surgical outcomes [42, 43]. Retrospective data imply associations with worse survival in patients who have blood transfusions and major complications, specifically in patients who have not had neoadjuvant therapy. Whether this is due to immunological effects due to untreated micro-metastatic disease and/or delays or omissions of adjuvant therapy has not been fully answered [44, 45]. The main conclusion is a successful operation is not judged solely on the pathology report, but rather the conduct of the operation itself and avoiding complications to obtaining what is recently being called "textbook outcomes," perhaps similar to shutouts in sports.

The definition of adjuvant therapy is different depending on if the patient had surgery upfront or had neoadjuvant therapy. If surgery is upfront, then there is no question that adjuvant therapy must be given if the patient is healthy enough. However, for the increasing proportion of patients between treated with neoadjuvant therapy, the question of additional postoperative therapy remains unanswered prospectively. In one large retrospective study, there seemed to be a positive effect seen from postoperative chemotherapy in anatomically and borderline resectable PDAC patients who had been treated with either FFX or GA [46]. Until there is a prospective trial that randomizes patients after resection to additional postoperative therapy vs. surveillance, the question of additional therapy after neoadjuvant therapy will remain biased by the provider making that decision.

Future Directions

Although one can argue that the PD has been arguably one of the most studied operations in surgery over the past decade, there still remain many improvements which may not necessarily be replicable in the operating room. System improvements must be made to increase the proportion of patients who are optimized before undertaking such a large physiologic hit. Centralization or regionalization to high-volume centers will need to finally take place, although this is unlikely in a free choice healthcare system as we have in the USA [47]. Finally, outcomes need to be meticulously studied at each center and within each state and region so that surgeons can have feedback for individual improvement. No multivariate analysis will ever account for surgeon variability and the important of individual surgeon improvement through outcomes analyses. These are some of the immediate steps to improve surgical outcomes for patients with PDAC in the coming years.

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12 Management of Resectable and Borderline Resectable Disease: Medical Oncology

Sunyoung Lee and Milind Javle

Introduction

Pancreatic ductal adenocarcinoma (PDAC) commonly presents at an advanced, unresectable disease stage. This year, an estimated 57,600 adults in the USA will be diagnosed with PDAC and 47,050 deaths will result [1]. Only 10% are detected at an early, surgically resectable disease. Their 5-year survival with current therapies is suboptimal at 30–40% [2]. Therefore, multimodality approaches that include neoadjuvant and post-operative adjuvant chemotherapy are critical options to consider along with surgical resection. The advent of high-resolution imaging has outlined definitions such as "resectable," "borderline resectable," and "locally advanced unresectable" PDAC phenotypes. These definitions and their management need to be individualized and will be discussed in the following sections.

Definition of Resectability

At the current time, modern imaging including contrast-enhanced, pancreas-protocol computerized tomography (CT) scan of the abdomen, thoracic imaging, detailed history and physical, tumor markers such as CA 19-9 level are adequate for preoperative evaluation. The role of endoscopic ultrasound for staging is limited. Multi-detector CT scan with protocols optimized for pancreatic imaging provides a detailed assessment of tumor approximation to superior mesenteric artery (SMA), the superior mesenteric vein (SMV) and SMV–portal vein confluence (SMV-PV), the celiac artery, and the hepatic artery [3]. CT imaging is also valuable to detect extra-pancreatic tumor dissemination and congenital arterial or venous variants. Resectable PDAC includes no abutment of SMA, celiac or hepatic artery, and ≤50° narrowing of SMV or SMV-PV (Fig. 12.1).

Adjuvant Therapy

PDAC is considered a systemic disease, even at an early resectable stage. This may explain why surgery as initial therapy for pancreatic cancer does not result in a cure for the majority of patients. There has not been any remarkable improvement in survival after resection over the past three decades. However, surgical morbidity and mortality have improved dramatically over the past decade and in high-volume centers, the perioperative mortality associated with pancreaticoduodenectomy is 1% [4]. A retrospective review of the National Cancer Data Base (2004–2014) included 5279 PDAC patients who had surgery alone and 4537 who received adjuvant

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_12

chemotherapy [5]. The primary surgical approach was Whipple procedure in 61% of pts. Adjuvant chemotherapy was associated with improved overall survival irrespective of disease stage when compared with those undergoing surgery alone (median overall survival for surgery alone was 14 months vs. 21 months, for those receiving adjuvant chemotherapy; $p < 0.001$). Although these figures support the use of adjuvant chemotherapy, these data suggest that in the real-world setting, the clinical impact of surgery and adjuvant therapy has been modest over the past three decades. Phase III adjuvant trials for PDAC are depicted in Table 12.1. As suggested here, we may have reached a plateau in terms of overall survival improvement with adjuvant chemotherapy for PDAC. Two recent adjuvant studies, the adjuvant nab-paclitaxel trial for PDAC (APACT) study with gemcitabine and nab-paclitaxel and PRODIGE trial with FOLFIRINOX are exceptions in this regard and suggest that better patient selection as a result of improved diagnostic staging may be accounting for the better survival figures in these two recent trials.

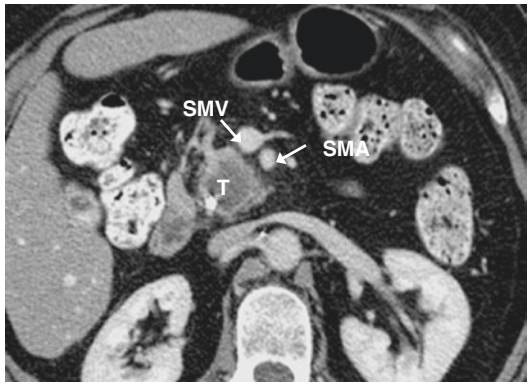

Fig. 12.1 Resectable pancreatic cancer

The APACT trial randomized 866 patients after resection to gemcitabine alone or gemcitabine with nab-paclitaxel [6]. The primary study endpoint was independent reviewer assessed progression-free survival (IR-PFS) and 866 patients were randomized. Median IR-assessed PFS was 19.4 months with the combination vs. 18.8 months with gemcitabine alone (HR, 0.88; $p = 0.1824$). Investigator-assessed PFS was 16.6 months vs. 13.7 months (HR, 0.82; $p = 0.0168$) in the study and control arms, respectively. Overall survival was 40.5 months vs. 36.2 months (HR, 0.82; 0.680—$p = 0.045$) in the study and control arms, respectively. This study although negative for its primary endpoint demonstrated that IR-PFS is not an appropriate endpoint in adjuvant PDAC as progression is often diagnosed on clinical grounds by treating clinician (such as by rising tumor markers or by increasing cancer related symptoms).

Conversely, the PRODIGE trial yielded a clinically and statistically meaningful improvement with modified-FOLFIRINOX chemotherapy as

Table 12.1 Phase III clinical trials of adjuvant therapy in pancreatic adenocarcinoma

Trial	Patients (*n*)	Treatment regimen	Median survival (*p* value)
GITSG [9]	43	Observation vs. chemoradiation	11 vs. 20 months (0.03)
RTOG 9704 [10]	538	Gemcitabine + chemoradiation vs. 5-fluorouracil + chemoradiation	17.1 vs. 18 months (0.12)
CONKO-001 [11]	354	Observation vs. gemcitabine	20 vs. 22.8 months (0.01)
ESPAC-1 [12]	289	Observation vs. chemotherapy vs. radiation	15.5 vs. 20.1 months (0.009)
ESPAC-3 [13]	1088	Fluorouracil vs. gemcitabine	23 vs. 23.6 months (0.39)
ESPAC-4 [14]	732	Gemcitabine + capecitabine vs. gemcitabine	28 vs. 25 months (0.032)
PRODIGE [7]	493	FOLFIRINOX vs. gemcitabine	51 vs. 35 months (0.003)
APACT [6]	866	Gemcitabine + nab-paclitaxel vs. gemcitabine	40.5 vs 36.2 months (0.045)

compared with gemcitabine in a phase III trial of 493 PDAC patients in France [7, 8]. The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group (H.R. 0.58; $p < 0.001$). The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (H.R 0.64; $p = 0.003$). This regimen is now considered as the standard of care as adjuvant therapy for PDAC patients with Eastern Co-operative Oncology Group (ECOG) performance status 0–1. In the above two trials, improved survival is noted both in the study and control arms as compared with historical controls. This improvement may also be on account of better patient selection for surgery, improved imaging techniques, and enhanced post-operative care.

Borderline Resectable PDAC

"Resectability" in PDAC requires lack of vascular involvement, particularly of the SMA, celiac and hepatic artery as described above and patent SMV-PV system [15]. Locally advanced and unresectable, however, included clinical presentations with significant vascular compromise. With increasing clinical experience, it became evident that there was a third, intermediate category where resection is still feasible in some cases with vascular reconstruction. This has now become possible due to multi-detector CT imaging that offers higher resolution images of the tumor vessel interface, with accurate assessment of the degree of abutment and encasement of adjacent vessels. Thus, tumors that have a limited degree of arterial abutment are now considered borderline resectable and are considered for neoadjuvant treatment protocols for tumor "downstaging" prior to resection (Fig. 12.2) [16]. Several systems have been proposed for classification of borderline resectable PDAC; the most recent International Consensus Guidelines are presented below [17]. These guidelines recognized that anatomical considerations by themselves could not determine resectability and both tumor biology and underlying medical conditions have to be accounted for within the classification.

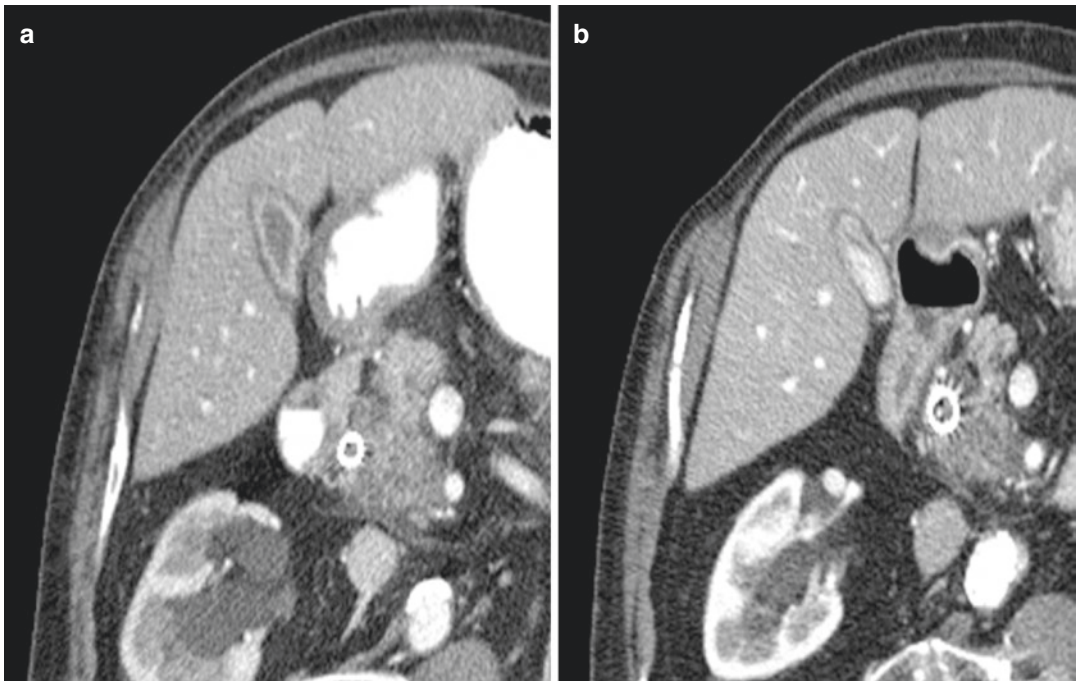

Fig. 12.2 Borderline resectable pancreatic cancer. (**a**) Before treatment. (**b**) After neoadjuvant therapy

The consensus guidelines defined patients with borderline resectable PDAC according to the three distinct dimensions: anatomical (A), biological (B), and conditional (C). Anatomic factors include tumor abutment with the superior mesenteric artery and/or celiac artery of less than 180°, tumor abutment with the SMV/SMV-PV but with proximal and distal ends amenable to reconstruction, this included bilateral narrowing or occlusion without extending beyond the inferior border of the duodenum. Biological factors include potentially resectable disease based on anatomic criteria but with clinical findings suspicious of distant metastases or regional lymph nodes metastases or serum carbohydrate antigen (CA) 19-9 level more than 500 units/ml. Conditional factors include the patients with potentially resectable disease based on anatomic and biologic criteria but with ECOG performance status of 2 or more. These patients are best treated with neoadjuvant therapy.

Neoadjuvant Therapy for PDAC

The rationale for neoadjuvant therapy for patients with resectable pancreatic cancer includes: (a) the potential for downstaging to maximize the chances of a margin-negative (R0) resection (b) treating micrometastatic disease early, (c) administering "adjuvant" therapy in a preoperative setting when it is better tolerated, and (d) using this approach to gauge the aggressiveness of the cancer and thereby select for surgery the patients who have the greatest likelihood of a favorable outcome. We have successfully completed five trials (Table 12.2) of neoadjuvant therapy for pancreatic cancer at the M.D. Anderson Cancer Center and our current treatment paradigm is based on the results of the same [18–21]. This is the largest reported single-center experience with neoadjuvant therapy for pancreatic cancer. Our studies have helped us stratify patients with surgically resectable cancer into two groups: (a) those who are likely to benefit from surgery (in our experience 75% of surgically resectable cases can undergo successful pancreaticoduodenectomy after neoadjuvant therapy) and (b) those for whom surgical resection is unlikely to be clinically beneficial (25% cannot undergo surgery after neoadjuvant therapy). In our recent study of neoadjuvant gemcitabine + radiation for patients with operable pancreatic cancer, the median survival duration was 34 months in patients who underwent surgical resection and 7 months in patients who did not [2]. The 5-year survival rates for those who did and did not undergo resection were 36% and 0%, respectively.

Table 12.2 Clinical trials of neoadjuvant therapy for pancreatic cancer at M.D. Anderson Cancer Center

	5-FU 50.4 Gy	5-FU 30 Gy	Paclitaxel 30 Gy	Gem-XRT	Gem-Cis XRT
No. of patients	28	35	37	86	90
Overall survival (mo)	NA	NA	12	23	17
No. who completed all treatment including PD (%)	17(60)	20(57)	20(54)	64 (74)	52 (66)
No. histologic response IIB-IV/total resected (%)	7 (41)	4 (20)	4/19 (21)	37(58)	31 (60)
No. SMA margin positive (%)	3 (18)	2 (10)	6/19 (32)	4(6)	1 (2)
No. death during treatment (%)	1 (4)	0	0	1 (1)	1 (1)
Median survival of patients who completed all treatment (mo)	NA	25	19	34	31
Median survival of patients who did not complete all treatment (mo)	NA	7	10	7.1	10.5

The use of neoadjuvant therapy in the case of borderline resectable PDAC is intuitive given the expectation that most but not all will undergo subsequent surgery. However, patients with borderline resectable disease are at a high risk for a margin positivity (R1) due to abutment with the vasculature, they require complex vascular reconstruction and have a high predilection for occult metastatic disease. As depicted in Table 12.2, an estimated 60–75% of patients receiving neoadjuvant therapy undergo subsequent resection. Prior neoadjuvant studies for PDAC are depicted in Table 12.3.

Majority of these studies were retrospective although some were prospective, single-arm trials. Until recently, there have been no randomized, prospective clinical trials of neoadjuvant therapy vs. upfront surgery.

The PREOPANC trial is the first randomized clinical trial of preoperative chemoradiotherapy vs. upfront surgical resection for resectable and borderline resectable PDAC [39]. This trial was conducted in 16 centers in Europe and 246 eligible patients were randomized to chemoradiotherapy, which consisted of three courses of gemcitabine, the second combined with 15 × 2.4 Gy radiotherapy, followed by surgery and four courses of adjuvant gemcitabine vs. immediate surgery and six courses of adjuvant gemcitabine. On intention to treat analysis, there was no median overall survival difference between the two arms [16.0 months with preoperative chemoradiotherapy and 14.3 months with immediate surgery (hazard ratio, 0.78; $p = 0.096$)]. A larger fraction of patients in the preoperative group received an R0 resection in the immediate surgery cohort ($P < 0.001$). Preoperative chemoradiotherapy was associated with significantly better disease-free survival and locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion.

As expected, not all patients receiving neoadjuvant therapy received surgical resection. Of the 119 patients who received neoadjuvant therapy, 72 (60%) were operated. This subgroup of patients with tumor resection followed by adjuvant treatment experienced a significantly improved median overall survival of 35.2 months in the preoperative chemoradiotherapy group and 19.8 months in the immediate surgery group (HR, 0.58; $p = 0.029$). The proportion of patients who suffered serious adverse events was higher in the neoadjuvant group 52% versus 41% ($P = 0.096$). Similar findings were reported by the ESCPAC-5 phase II trial where 90 patients with borderline resectable PDAC were randomized to immediate surgery, or neoadjuvant gemcitabine with capecitabine, FOLFIRINOX, or chemoradiation [40]. One year survival rate was 40% for immediate surgery and 77% for neoadjuvant therapy. Log-rank analysis showed an HR = 0.27, $p < 0.001$ in favor of neoadjuvant therapy.

These randomized clinical trials confirmed several points noted earlier in the prior non-randomized trials: (1) Neoadjuvant therapy offers survival advantage over upfront resection for PDAC patients with non-progressive disease after chemoradiotherapy, (2) neoadjuvant therapy is the preferred option for borderline resectable disease, and (3) chemoradiotherapy results in higher toxicity but this does not preclude surgery.

Role of Neoadjuvant Chemotherapy without Radiation

Neoadjuvant chemotherapy alone, without radiotherapy was examined in the prospective phase II SWOG 1505 clinical trial [41]. In this study, 147 patients with resectable PDAC were randomized to preoperative FOLFIRINOX or gemcitabine and nab-paclitaxel. Each treatment arm included the same regimen administered post-operatively and the primary study endpoint for 2-year overall survival. Resection was successfully performed in 70% of the patients who received neoadjuvant therapy. The two-year survival was similar (42% with FOLFIRINOX and 48% with gemcitabine and nab-paclitaxel, $p = 0.12$). There were no significant median overall survival differences between the two arms. At the current time, there are insufficient data to recommend chemotherapy vs. chemoradiotherapy as the preferred neoadjuvant modality prior to resection.

Table 12.3 Prior studies of resectable pancreatic cancer

Study	N	Type of neoadjuvant therapy	Resection rate	Median survival (months)
Ammori et al. (2003) [22]	67	Chemoradiation	9 (13%) R0: 6 (9%)	17.6 (surgery); 11.9 (no surgery)
Katz et al. (2008) [16]	160	Chemoradiation	66 (41%) R0: 62 (39%)	40.0 (surgery); 13.0 (no surgery)
Marti et al. (2008) [23]	26	Chemotherapy Chemoradiation	4 (15%)R0: 3 (11%)	13.0 (all patients); 12.0–62.0 for resected group
Massucco et al. (2006) [24]	28	Chemoradiation	8 (29%)R0: 7 (25%)	>21.0 (surgery); 10.0 (no surgery)
Landry et al. (2010) [25]	21	Chemotherapy Chemoradiation	5 (24%)R0: 3 (14%)	26.3 (surgery)
Brunner et al. (2008) [26]	12	Nelfinavir chemoradiation	6 (50%)R0: 6 (50%)	NA
Leone et al. (2012) [27]	39	Chemotherapy chemoradiation	11 (28%) R0: 9 (23%)	31.5 (surgery); 12.3 (no surgery)
Chun et al. (2010) [28]	74	Chemoradiation	74 (all patients) R0: 44 (59%)	23 (surgery); 15 (no surgery)
Stokes et al. (2011) [29]	41	Chemoradiation	16 (46%) R0: 12 (29%)	23 (surgery); 12 (no surgery)
Lee et al. (2012) [30]	18	Chemotherapy	15 (83%) R0: 13 (72%)	23.1 (surgery); 13.2 (no surgery)
Kang et al. (2012) [31]	67	Chemoradiation	32 (48%) R0: 28 (41%)	26.3 (surgery)
Takahashi et al. (2013) [32]	80	Chemotherapy Chemoradiation	43 (54%) R0: 43 (54%)	25 (surgery)
Chuong et al. (2013) [33]	57	Chemotherapy Chemoradiation	32 (56%) R0: 31 (54%)	19.3 (surgery)
Kim et al. (2013) [34]	39	Chemotherapy Chemoradiation	24 (62%) R0: 21 (54%)	25 (surgery)
Rose et al. (2014) [35]	64	Chemotherapy	31 (48) R0: 27 (42%)	23.6 (all patients); 15.4 (no surgery)
Golcher et al. (2015) [36]	66 (33 upfront, 33 neoadjuvant)	Chemotherapy Chemoradiation	R0: 17 (52%) R0: 16 (48%)	17.4 (neoadjuvant) 14.4 (upfront surgery)
Jang et al. (2018) [37]	35 (17 upfront, 18 neoadjuvant)	Chemotherapy Chemoradiation	R0: 14 (82%) R0: 6 (33%)	21 (neoadjuvant) 12 (upfront surgery)
Motoi et a. (2019) [38]	362 (180 upfront, 182 neoadjuvant)	Chemotherapy	NA	36.7 (neoadjuvant) 26.6 (upfront surgery)

Our treatment paradigm for resectable and borderline resectable disease, outside of a clinical trial includes a sequential approach of systemic chemotherapy, followed by chemoradiation and subsequent surgical resection. For patients who are not enrolled in a clinical trial, we offer induction chemotherapy with FOLFIRINOX or gemcitabine with nab-paclitaxel for 8 weeks followed by restaging CT scans. A multi-disciplinary decision follows regarding subsequent plan for systemic chemotherapy or consolidative chemoradiation. For patients experiencing a definite radiological response and robust CA 19-9 decrement, further chemotherapy is offered. Others without a radiologic response or with stable disease are offered chemoradiation. Patients experiencing systemic disease progression with distant metastases are no longer considered as surgical candidates and are offered second-line chemotherapy or clinical trials.

Radiation therapy along with concurrent 5-fluorouracil or capecitabine is typically administered in a dose of 50.4 Gy to the pancreatic head, body, or tail (depending on the tumor location) along with the vasculature: celiac artery, SMA, and SMV. Thus, the field targets area of local spread; in addition, only suspicious nodes are targeted and not the entire nodal basin which also spares toxicity. Restaging CT scans are typically obtained 6–8 weeks after completion of chemoradiation and before planned surgical resection.

Locally Advanced PDAC

These cancers would typically be considered as unresectable and are treated with systemic chemotherapy, sometimes followed by consolidative chemoradiation. Recently, locally advanced PDAC has been further subclassified into types A and B [42, 43]. Type A includes higher degree of SMA, hepatic arterial, or celiac abutment that is still amenable to vascular reconstruction, whereas type B is unresectable. This segregation has resulted from the fact that some patients with lower vascular compromise experience radiological improvement after multiagent chemotherapy and radiation. The type of surgery required includes complex vascular reconstruction and accompanied with morbidity and mortality and should be restricted to high-volume centers.

What Is the Role of Radiotherapy in the Neoadjuvant Setting for PDAC?

Iacobuzio-Donohue and colleagues demonstrated in rapid autopsy series that 30% of patients with PDAC die of local invasion and not distant failure [44]. It is important to note that most local recurrences develop within millimeters of the SMA and celiac artery because these vessels are immediately adjacent to a surgical margin and PDAC frequently extends along the perivascular nerves. Local control is therefore an important goal of therapy and is facilitated by radiotherapy. There has been one randomized, controlled trial to our knowledge investigating the role of radiotherapy vs. chemotherapy alone for PDAC.

The locally advanced PDAC (LAP07) phase 3 randomized trial enrolled 449 patients with locally advanced, unresectable disease who received gemcitabine ± erlotinib alone or followed by consolidative chemoradiation with 50.4 Gy [45]. The primary outcome was overall survival and there was no significant survival difference between the chemotherapy vs. chemoradiation arms. However, chemoradiotherapy was associated with decreased local progression (32% vs 46%, $P = 0.03$) and no increase in grade 3 to 4 toxicity, except for nausea. Although LAP07 was a study for unresectable locally advanced PDAC, the study results suggest that an improvement in local control from radiotherapy may result in incremental clinical benefit in earlier stage PDAC. Conventional external beam radiotherapy was used in this trial. However, there may be clinical advantages with the use of Intensity Modulated Radiation Therapy (IMRT) or Stereotactic Body Radiotherapy (SBRT), which can provide high doses over short periods of time. Phase II trials of SBRT suggest this approach is feasible and results in clinical benefit. Herman et al. treated 49 patients with locally

advanced PDAC with gemcitabine followed by SBRT (33.0 gray [Gy] in 5 fractions) [46]. After SBRT, patients received maintenance therapy with gemcitabine till progression. The median overall survival was 13.9 months and 80% were free of local disease progression. These encouraging data led to the Alliance A021501 trial of neoadjuvant SBRT followed by surgical resection for borderline resectable PDAC [47]. This study was unfortunately discontinued as on interim analysis, futility boundary for R0 resection was reached. SBRT may be potentially inferior to chemoradiotherapy as concurrent chemotherapy may offer a systemic antitumor effect. Neoadjuvant SBRT cannot be recommended at this time for resectable or borderline resectable PDAC outside the context of a clinical trial. However, concurrent chemoradiotherapy in a dose of 50.4 Gy is commonly used in our practice at MD Anderson Cancer Center along with capecitabine in the neoadjuvant setting for resectable and borderline resectable PDAC.

Histopathologic Assessment Following Neoadjuvant Therapy

Histopathologic assessment of the PDAC specimen after neoadjuvant therapy is complicated. The current College of American Pathology (CAP) grading for tumor response assessment is uniform across several cancers including esophagus, stomach, pancreas, and rectum. The assessment compares residual tumor with background fibrosis as follows: Grade 0, no viable residual tumor (pathologic complete response); Grade 1, marked response (minimal residual cancer with single cells or small groups of cancer cells); Grade 2, partial response (residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells); and Grade 3, poor or no response (extensive residual cancer with no evident tumor regression). This grading scheme for tumor response is the same as those used for carcinomas of esophagus, stomach and rectum in the current CAP protocols. However, there has been very limited prognostic validation of this grading and our retrospective data indicate no survival differences between grades 3 and 4. Therefore, we have proposed an alternative three-tier system as below: Histologic tumor response grade (HTRG) 0, no viable residual tumor (pathologic complete response); HTRG 1, marked response (less than 5% viable tumor cells, minimal residual cancer with single cells or small groups of cancer cells); HTRG 2, moderate to poor response (≥5% residual tumor cells). This system has been validated in a cohort of 223 PDAC resection specimens after prior neoadjuvant therapy [48, 49].

Tumor Surveillance in PDAC Using Circulating DNA (ctDNA)

CA19-9 is the most commonly used marker in pancreatic cancer with a sensitivity and specificity of 79–81% and 82–90%, respectively [50, 51]. However, it is not useful as a screening marker with a low positive predictive value (0.5–0.9%) and does not accurately predict prognosis [52, 53]. It is commonly elevated in other diseases such as biliary obstruction, cholangitis, and pancreatitis [54, 55], complicating clinical assessment of pancreatic cancer.

Tumor-specific DNA mutations can be detected in the cell-free component of peripheral blood in patients with advanced cancer [56]. This circulating tumor DNA (ctDNA) allows for non-invasive molecular characterization of tumors that provides indication to targeted therapies [57–59]. In addition to this therapeutic role, ctDNA has been supported as a biomarker and an independent prognostic marker in pancreatic adenocarcinoma. In a study of 104 patients with advanced pancreatic cancer, 50% of patients had detectable ctDNA levels, and 45% and 42.3% of patients revealed *TP53* and *KRAS* mutation. This study showed worse overall survival (8.4 vs. 16 months, $p < 0.0001$) and progression-free survival (3.2 vs. 7.9 months, $p < 0.0001$) in patients with ctDNA positive patients, compared with negative patients [52].

Another study validated a role of ctDNA as a prognostic marker in 112 patients with localized pancreatic cancer. Positive ctDNA detection in

the pre- and post-operative settings was associated with worse recurrence-free survival and overall survival. All the patients (13/13, 100%) with detectable ctDNA post-operatively had recurrence, and seven patients had recurrence while receiving gemcitabine-based adjuvant chemotherapy [60]. A meta-analysis of ctDNA in patients with resectable pancreatic adenocarcinoma confirmed that patients with detectable ctDNA had a higher risk for disease recurrence than those without detectable ctDNA (pre-surgery, HR 1.96, 95% CI 0.65–5.87; post-surgery HR 2.20, 95% CI 0.99–4.87).

Obtaining a sufficient biopsy tissue for molecular or pathology tests is often times not feasible in localized pancreatic cancer. For example, fine needle aspiration via endoscopic ultrasound or resection of pancreatic tumors with less viable cells status post-neoadjuvant chemotherapy sometimes provides insufficient tissues for molecular tests [61]. In this clinical scenario, ctDNA can be useful and lead to identification of actionable mutations, offering more therapeutic options such as targeted therapy or clinical trials. These mutations include cMET (2.5%), FGFR2 (1.2%), NTRK fusion (6%), mTOR (2%), or HER2 expression and amplification (2–6%) [62].

Neoadjuvant Therapy Followed by Metastasectomy for PDAC

Metastasectomy of an oligometastatic disease with liver or lung lesions has resulted in survival benefit in other cancer types. More than 50% of patients with colorectal cancer present with a metastatic disease at baseline, and the most common metastatic sites are the liver and lungs [63]. Resection of metastatic liver lesions offers five-year survival rate ranging from 24% to 58% [64, 65], while systemic chemotherapy alone has 10–11% [66]. Pulmonary metastasectomy is also considered for surgically fit patients with resectable lung metastases, and it confirmed survival benefit [67, 68].

The tumor biology of pancreatic adenocarcinoma is generally more aggressive than that of colorectal cancer for which liver and lung metastasectomy has offered survival benefit. In pancreatic adenocarcinoma, up to 12% of patients with no radiologic evidence of metastases in the pre-operative setting are later found to have liver or peritoneal metastases in the exploratory laparoscopy [69]. Survival benefit from metastasectomy is conflicting, and there have been no randomized controlled trials to clearly define clinical outcomes after metastasectomy [70]. The NCCN guideline does not recommend surgical resection in cases of distant metastases [71]. Surgery of the primary pancreatic tumor is challenging with a mortality rate ranging from 7.3% to 22.9% (5% in high-volume centers) [72, 73]. Therefore, synchronous (or even metachronous) resection of the primary pancreatic tumor and metastatic lesions can lead to a higher mortality rate. The liver is the most commonly affected metastatic site from pancreatic adenocarcinoma with the peritoneum and lungs following [57, 74], and many studies of hepatic metastasectomy have been published.

In a retrospective analysis of 6 European pancreas centers, 69 patients underwent synchronous resection of liver metastatic lesions and the primary pancreatic tumor, and clinical outcomes were compared with the other 69 patients who only underwent surgical exploration without tumor resection. Overall survival appeared to be prolonged in the group of resected patients (14 vs. 8 months, $p < 0.001$). Patients with a primary tumor in the head of the pancreas had survival benefit, but those with the tumor in the body or tail of the pancreas did not (14 vs. 15 months, $p = 0.31$). Although this study showed a clear survival benefit in patients who had synchronous resection of hepatic lesions and the primary tumor in the head of the pancreas, a strong conclusion cannot be drawn due to the limitations of retrospective study and a potential for selection bias [75].

Crippa et al. also investigated clinical outcomes in patients who received neoadjuvant chemotherapy followed by surgical resection of liver metastatic lesions. This study included 127 patients who received systemic chemotherapy including gemcitabine. Chemotherapy response rate was 44% (7% complete response and 37% partial response). After 12 months from the initial

diagnosis, surgical resection was performed for 11 patients. In this subgroup, median survival was longer (46 vs. 11 months, $p < 0.0001$) for patients undergoing resection. Of note, patients who received multiple chemotherapeutics (HR, 0.512) and surgical resection (HR, 0.360) had longer overall survival, while those with more than 5 metastatic lesions (HR, 3.515) and CA19-9 reduction less than 50% (HR, 2.708) had shorter overall survival. This study demonstrates a subset of patients with good response from chemotherapy may potentially benefit from surgical resection of the metastatic and primary pancreatic tumors [76].

Patients with isolated pulmonary recurrence are known to have better overall survival [77]. A study of 40 patients with isolated pulmonary recurrence showed median survival of 22.5 months (95% CI 19.1–31.8) after diagnosis of pulmonary metastasis. Patients with less than 10 lung metastases (31.3 vs. 18.7 months, $p = 0.003$) and a unilateral localization of lung involvement (31.3 vs. 21.8 months, $p = 0.03$) had longer survival [78]. In a retrospective study of 31 patients with isolated lung metastasis, nine patients underwent surgical resection after pulmonary recurrence. The median time from the resection of the primary pancreatic tumor to pulmonary metastasis was 34 months. The median overall survival was longer in patients who had pulmonary metastasectomy than those who did not (51 vs. 23 months, $p = 0.04$). Median relapse-free survival was 29 vs. 14 months ($p < 0.001$). There was a trend toward greater 2-year survival after relapse in the patient group with pulmonary metastasectomy, compared with those who did not undergo surgery (40 vs. 27%, $p = 0.2$) [79].

Above studies demonstrate that metastasectomy can be performed in PDAC in patients with favorable biology and response to systemic chemotherapy [70]. Patients with isolated, metachronous pulmonary metastasis after prior pancreatectomy have experienced clinical benefit including improved survival [79]. However, there have been no randomized clinical trials or prospective studies to better assess survival outcomes from metastasectomy in patients with stage IV pancreatic adenocarcinoma. At this point, the NCCN does not recommend surgical resection in patients with metastatic pancreatic adenocarcinoma. In our practice, we will consider resection of isolated, metachronous pulmonary metastases in patients who have undergone prior pancreatic surgery although this cannot be regarded as standard of care.

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13 Management of Resectable and Borderline Resectable Disease: Radiation Oncology

Emma B. Holliday, Eugene J. Koay, Cullen M. Taniguchi, and Albert Koong

Introduction

Historically, radiation therapy has been utilized in the postoperative setting for the treatment of pancreatic cancer. When given postoperatively, doses of radiation are limited to 45–54 Gray (Gy) and delivered in 1.8–2.0 Gy fractions over 5–6 weeks. This is because the luminal gastrointestinal organs of the upper abdomen are inherently radiosensitive, and increased dose leads to unacceptable risk of serious normal tissue toxicity when using standard techniques [1]. The classic paradigm may be shifting and indications for radiation may be increasing. Recently, there is more interest in a multidisciplinary preoperative approach for patients with resectable or borderline resectable tumors [2]. Additionally, new technologic advances have made ablative, and perhaps even curative, radiation doses achievable for certain patients. This comes from several improvements over the past 15–20 years which have made it possible to better conform the prescription dose to the intended target volumes. This increased conformality allows for a reduction in toxicities and improvement in treatment adherence, toxicities, and patient quality of life [3].

While conventional radiotherapy techniques used X-ray imaging and bony anatomic landmarks to estimate the position of the pancreas in the upper abdomen, modern 3D imaging techniques are better able to visualize soft-tissue targets as well as adjacent luminal organs at risk for toxicity. This paradigm shift was paved by improvements in target delineation, immobilization, treatment planning, and image-guided treatment delivery. Dose escalation has been safely achieved with hypofractionated or stereotactic techniques, which may offer ablative options to those who are not candidates for curative surgery [4]. Further, investigations into ion therapy, including proton and carbon beam therapy, seek to further optimize dosimetry which may allow further escalation of dose to the tumor target while better sparing normal tissue from toxicity.

This chapter seeks to outline current indications for radiation in the adjuvant, neoadjuvant, and definitive settings. Next, specific technologic advances that seek to improve the accuracy, efficacy, and toxicity profile of pancreas-directed radiotherapy will be described, including imaging and target delineation, internal motion management as well as advanced image-guided radiation therapy. Finally, specific radiation techniques and modalities will be discussed, including intensity-modulated radiation therapy,

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_13

hypofractionated schedules, stereotactic body radiotherapy, and particle beam therapies.

Indications for Radiation

Adjuvant Radiation

A Whipple procedure, or pancreaticoduodenectomy, is an extensive operation with significant risks for postoperative morbidity and mortality. Even after such an extensive surgery, the 5-year overall survival (OS) after surgery alone is only 6% [5]. Although adjuvant chemotherapy has been shown to improve survival [6], data have been conflicting with regard to the benefits of postoperative radiation. In the 1970s, the Gastrointestinal Tumor Study Group (GITSG) conducted the first randomized, prospective study to evaluate the potential benefit of adjuvant chemoradiation [7]. The chemoradiation regimen was a split course given as two courses of 20 Gray (Gy), each separated by a 2-week break. Fluorouracil was given at the beginning of each course of radiation and was continued weekly for 2 years or until recurrence. The fields were large (up to 400 cm^2), not shaped, and consisted of anteroposterior and posteroanterior beams. Despite using doses and techniques that are antiquated by current standards, the results of this study showed a significant improvement in median survival with adjuvant chemoradiation compared with surgery alone (20 months versus 11 months; $p = 0.035$). It should be noted that the study was closed prematurely for both slow accrual as well as a notable difference in survival noted after enrolling only 43 of a planned 100 patients. Although specific radiation toxicities were not mentioned, the authors did note that there were no grade 4 or 5 toxicities attributable to chemoradiation [7]. Since the GITSG trial, there has not been another published study so clearly demonstrating a survival benefit for adjuvant chemoradiation.

However, two studies subsequently performed in Europe showed conflicting conclusions. The European Organization for Research and Treatment of Cancer (EORTC) study randomized patients with periampullary and pancreatic cancer to surgery alone or surgery and adjuvant chemoradiation [8]. This study was five times larger than the GITSG trial with 218 patients randomized. As analyzed, the median survival was not statistically significantly different at 19 months with surgery alone versus 24.5 months with adjuvant chemoradiation (1-sided $p = 0.208$). There are several caveats to this study. For one, the statistical methods have been called into question [9]. Additionally, patients with periampullary cancers were included, and this group has a better prognosis regardless of therapy. Additionally, adherence to the prescribed adjuvant regimen was poor; 20% of patients assigned to adjuvant chemoradiation did not receive any treatment, and compliance to chemotherapy per protocol was only 50%. Despite these caveats, this study showed no benefit to adjuvant chemoradiation with long-term follow-up [10]. The European Study for Pancreatic Cancer (ESPAC-1) trial was another large randomized study that utilized a 2 × 2 factorial design comparing postoperative observation, chemotherapy, chemoradiation, and chemoradiation followed by chemotherapy. Chemotherapy alone was associated with improved 5-year survival (21% vs 8%; $P = 0.009$), and chemoradiation was associated with inferior survival (10% vs 20%; $P = 0.05$) [11]. As with the EORTC study, adherence with the assigned study therapy was poor. Thirty-three percent did not complete chemotherapy and 17% received no chemotherapy at all. The sequential nature of the treatments dictated by the 2 × 2 factorial design was also discussed as a major confounding factor [12].

While the results of the EORTC and ESPAC-1 studies were largely responsible for a shift in practice away from adjuvant chemoradiation in Europe, it continued to be explored in the USA. Chemoradiation with relatively modern techniques (continuous, rather than split course delivered to a total dose of 50.4 Gy) was included in both arms of the Radiation Therapy Oncology Group (RTOG) 9704 trial in which the randomization was between gemcitabine vs 5-FU before and after CRT [13]. One significant revelation from this study was that adherence to protocol-specified radiation guidelines was associated with improved survival and nonadherence was associated with a trend towards increased G4/5 nonhematologic toxicity [14]. This emphasized

the importance of careful radiation planning in both the efficacy and toxicity of this adjuvant treatment. RTOG 0848 addressed the question of whether there is specific benefit of adjuvant chemoradiation given in the modern era. RTOG 0848 asked two clinical questions: (1) does adding erlotinib to gemcitabine as adjuvant therapy improve overall survival and (2) does adding 5-FU based chemoradiation to adjuvant chemotherapy improve overall survival. The results of the erlotinib randomization were recently published, and the addition of erlotinib did not provide a signal for increased survival [15]. These results are in line with what was found in the LAP 07 trial as well [16]. Currently, we are still waiting for results of the chemoradiation randomization to mature and there have been no published results to date. When we do obtain these results, it is also important to realize, however, that modified FOLFIRINOX or a gemcitabine doublet therapy is now the standards of care for the adjuvant setting [2].

Neoadjuvant Radiation

The paradigm for the multidisciplinary treatment of pancreatic cancer is shifting to favor preoperative, rather than postoperative, therapy. The rationale is similar to what has been demonstrated in rectal cancer, where preoperative therapy is better tolerated and seems to have oncologic benefits in terms of local control [17]. Biologically, radiation and chemotherapy may be more effective in the preoperative setting when the tumor's blood supply is intact. For an aggressive entity such as pancreatic cancer in which rates of distant metastases are so high, neoadjuvant therapy provides the additional benefit of allowing for some patient selection on the basis of tumor biology. Those who progress or metastasize on neoadjuvant therapy could be spared the morbidity of a major operation [18]. Finally, as evidenced by the compliance rates with postoperative treatment in the adjuvant trials discussed above, it is clear that many patients have a difficult time tolerating systemic therapy due to challenges with postoperative healing, nutrition, or overall performance status. Current NCCN guidelines recommend neoadjuvant therapy for borderline resectable disease and consideration of neoadjuvant therapy even in the setting of resectable disease [2].

The case for maximal neoadjuvant therapy in the treatment of borderline resectable pancreatic cancer is straightforward. When chemotherapy is not sufficient to downstage patients such that an R0 resection is feasible, neoadjuvant chemoradiation is often considered, particularly given the poor prognostic implications of an R1 resection [19]. Over the last 30 years, increasing numbers of retrospective and prospective single arm studies have described the safety and efficacy of this approach. Evans and colleagues first published on the MD Anderson experience using 50.4 Gy in 28 fractions with concurrent 5-FU in the preoperative setting. Seventeen of the initial 28 patients treated went on to receive surgery [20]. Subsequent publications from this group combined different chemotherapy regimens with preoperative radiation all showing high rates of R0 resection, acceptably low toxicity and postoperative complication rates [21–26]. Mehta and colleagues from Stanford also published their experience with preoperative chemoradiation consisting of 50.4–56 Gy in 1.8–2 Gy fractions delivered with 5-FU. Nine of 15 borderline resectable patients were able to go on to surgical resection, and two of nine had a pathologic complete response. Median survival in the group that underwent surgery was 30 months [27]. Sequencing neoadjuvant chemoradiation after initial chemotherapy may be a superior preoperative multidisciplinary treatment sequence. The Alliance for Clinical Trials in Oncology published a small feasibility study in 2016 in which 14 institutions enrolled 29 patients with borderline resectable pancreatic adenocarcinoma to a single arm trial in which they received four cycles of modified FOLFIRINOX followed by capecitabine-based chemoradiation to 50.4 Gy in 28 fractions prior to pancreatectomy [28]. Sixty-eight percent of patients successfully went on to surgery, and 93% of those had an R0 resection. Further, 33% of patients who underwent pancreatectomy had <5% residual cancer cells and 13% had a pathologic complete response. The median OS of enrolled patients was 21.7 months [28].

The first randomized study to formally evaluate preoperative chemoradiation for borderline resectable pancreatic cancer was the Korean phase 2/3 study led by Jang and colleagues [29]. In this study, 58 patients were randomly assigned to either gemcitabine-based chemoradiation to 54 Gy in standard fractionation prior to surgery or surgery followed by chemoradiation. The R0 resection rate was nearly doubled in the neoadjuvant chemoradiation group (51.8% vs 26.1%; $P = 0.004$). Two-year and median OS were also better in the neoadjuvant chemoradiation group (40.7% vs 26.1% and 21 mo vs 12 mo, respectively; $p = 0.028$). The study was halted after 58 of a planned 110 patients given the degree of superiority for neoadjuvant treatment [29]. The Dutch PREOPANC-1 study showed similar advantages to neoadjuvant treatment, albeit with a slightly different trial design. The experimental arm consisted of three cycles of preoperative gemcitabine with 36 Gy in 15 fractions given with cycle two followed by another four cycles of gemcitabine after surgery. The control arm consisted of upfront surgery followed by six cycles of adjuvant gemcitabine. The R0 resection rate was significantly better with preoperative treatment (71% vs 40%; $P < 0.001$). Additionally, there was an improved disease-free survival and locoregional failure-free interval for patients receiving preoperative therapy. However, there was no difference in overall survival between the two groups (median survival 16 vs 14.3 months; $P = 0.096$). There was a predefined subset analysis of patients who actually started their postoperative chemotherapy, and those patients did have a significant survival benefit compared with patients who received surgery upfront (35.2 vs 19.8 months; $P = 0.029$). The authors conclude this suggests a clinically meaningful benefit for preoperative chemoradiation, though further studies are needed.

Taken in totality, results from retrospective and prospective studies suggest that neoadjuvant chemoradiation is superior to an upfront surgery approach. However, it is not clear from currently published data what the optimal neoadjuvant regimen should be. A recent meta-analysis suggested improved R0 resection rates with neoadjuvant chemoradiation compared with neoadjuvant chemotherapy, but overall survival was superior with neoadjuvant chemotherapy [30]. Given the absence of prospective comparative data, the choice of preoperative therapy varies regionally. There is much enthusiasm for neoadjuvant chemotherapy prior to surgery, particularly in Europe [31]. To truly evaluate the value of neoadjuvant chemoradiation in the modern era, comparisons with modern chemotherapy such as FOLFIRINOX are needed. Currently, the NorPACT-1 trial is investigating upfront surgery vs preoperative modified FOLFIRINOX chemotherapy followed by surgery [32], the PANACHE01-PRODIGE48 trial is comparing preoperative FOLFIRINOX vs FOLFOX [33], and the PREOPANC-2 trial is comparing the gemcitabine chemoradiation arm of PREOPANC-1 with preoperative modified FOLFIRINOX. Additionally, the Alliance for Clinical Trials in Oncology Trial A021101 compared eight cycles of preoperative modified FOLFIRINOX chemotherapy with seven cycles of modified FOLFIRINOX plus stereotactic body radiotherapy [34]. Results of these studies are eagerly anticipated to determine the best composition and sequence of preoperative therapies.

Definitive Radiation

Up to 30% of patients with newly diagnosed pancreatic cancer are unresectable at diagnosis [35]. This is typically defined as more than 180° encasement of the celiac axis or superior mesenteric artery, portal vein or superior mesenteric vein involvement that cannot be reconstructed, or nodal disease that extends beyond the typical plane of resection [2]. Extrapolated from data in the metastatic setting [36, 37], multi-agent chemotherapy either with FOLFIRINOX or gemcitabine + nab-paclitaxel is the current standards of care for patients with locally advanced, inoperable pancreatic cancer. However, current guidelines also list consolidation chemoradiation or SBRT after initial chemotherapy as appropriate first line therapy [2]. The role of radiation in the treatment of locally advanced pancreatic cancer has been debated since the 1980s. The results of

five randomized trials in the past four decades have been mixed. Some early studies showed worsened toxicity without survival benefit [38, 39], others showed an improvement in survival with combined modality therapy [40, 41], while one study showed a survival decrement with the addition of radiation [42].

None of these studies, however, studied the role of radiation after a period of induction chemotherapy until the LAP07 international phase 3 trial was published in 2016 [16]. This study asked two questions: first, whether the addition of erlotinib to gemcitabine would improve OS, and second, whether the addition of consolidative chemoradiation (54 Gy in 30 fractions with concurrent capecitabine) delivered to patients who did not progress after four months of chemotherapy would improve OS. Median survival was 15.2 months with the addition of chemoradiation and 16.5 months with chemotherapy alone. Neither the addition of chemoradiation nor the addition of erlotinib was associated with improved OS, but the addition of chemoradiation was associated with decreased local progression and a longer interval without chemotherapy. With the exception of nausea, there was no increase in G3-4 toxicities with the addition of chemoradiation [16]. The major limitation of this study is that the chemotherapy given on LAP07 is no longer considered standard of care. With improved systemic control with more effective chemotherapies, the local control benefits of radiation may lead to improved OS. Additionally, there is increasing evidence that dose-escalated radiation regimens may improve OS for patients with inoperable pancreatic cancer.

There have been several retrospective reports published showing improved LC and OS with radiation dose escalation of varying fractionation schedules. Chung and colleagues published a retrospective review of 497 patients with locally advanced pancreatic cancer. Patients who received a total dose ≥61 had higher OS and local failure-free survival. This difference is persistent even after propensity score matching [43]. Krishnan and colleagues published a retrospective study of 200 patients with locally advanced pancreatic cancer treated with consolidative chemoradiation after induction chemotherapy. In this study, tumors >1 cm from luminal GI organs were treated with dose-escalated IMRT to a BED above 70 Gy. For reference, 50.4 Gy in 28 fractions has a BED of 59.47 Gy. Patients receiving >70 Gy BED had a longer median survival (17.8 vs 15 mo; $P = 0.03$) and improved 3-year OS (31% vs 9%) [44]. This suggests that improved LC may indeed be translated to an improved OS for select patients after systemic therapy. Regimens to achieve a BED >70 Gy include 63–70 Gy in 28 fractions (BED 77.18–87.5), 60–67.5 Gy in 15 fractions (BED 78–97.88), and 40–50 Gy in 5 fractions (BED 72–100) [45]. Figure 13.1 shows dose-escalated definitive radiation for an unresectable pancre-

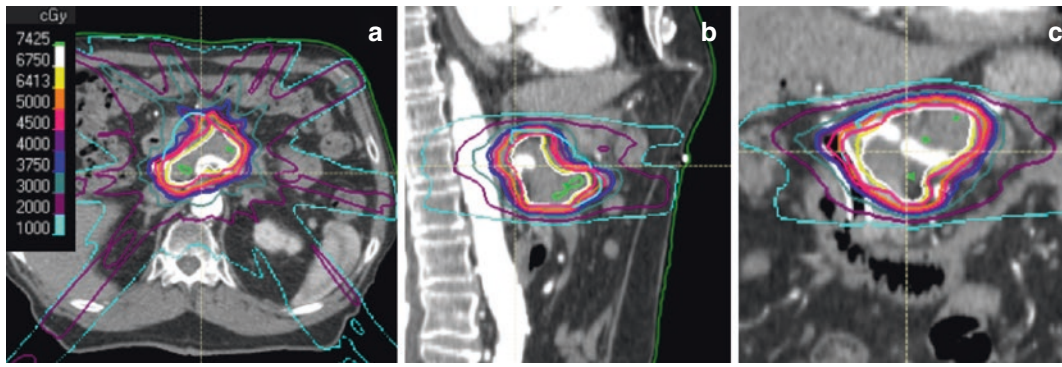

Fig. 13.1 This figure shows representative axial (**a**), sagittal (**b**), and coronal (**c**) images from the radiation plan for patient with unresectable adenocarcinoma of the head of the pancreas treated definitively to a total dose of 67.5 Gy in 15 fractions with concurrent daily capecitabine

atic adenocarcinoma in which 67.5 Gy was delivered in 15 fractions. Advanced technologies in treatment planning, respiratory motion management, and daily image guidance are essential to achieving dose escalation [45, 46], and these will be discussed in further detail in the next section.

Several ongoing trials seek to evaluate the benefits of dose-escalated radiation in the treatment of locally advanced pancreatic cancer. SCALOP-2 is a randomized phase 2 trial with a safety run-in phase. All patients receive three cycles of gemcitabine and Abraxane, and those with stable or responding disease are eligible to be randomized to one of five arms: capecitabine-based chemoradiation to either standard (A + B) or high (C + D) dose with (A + C) or without (B + D) the addition of nelfinavir or no radiation and three more cycles of chemotherapy (E). The standard dose radiation is 50.4 Gy in 28 fractions and the dose-escalation regimen is 60 Gy in 30 fractions (BED 72) [47]. Several small ongoing or recently completed trials have evaluated dose-escalated SBRT at doses ranging from 40 to 60 Gy in 3–5 fractions [48–50]. Forthcoming results will be helpful in tailoring therapy for patients who are not candidates for surgical resection.

The Impact of Advanced Technologies in Radiation Delivery

Imaging and Target Delineation

In the past, radiotherapy targets were defined with manually drawn treatment fields on portal images taken in treatment position at the beam's eye view. Modern radiotherapy for pancreatic cancer includes the routine use of advanced diagnostic imaging and treatment simulation with computed tomography (CT) for target delineation and treatment planning as endorsed by the National Comprehensive Cancer Network (NCCN) [2].

Whereas CT-based simulation is executed by immobilizing the patient in treatment position and obtaining computerized tomography, MRI- or PET-based simulation can involve either (1) obtaining diagnostic-quality imaging in treatment position and performing sophisticated image fusion with CT-simulation or (2) obtaining MRI- or PET-imaging in place of CT-based simulation on a dedicated diagnostic-quality simulator. Target delineation is further aided by fusion and deformable co-registration software which can merge PET, MRI, or other diagnostic imaging to CT-simulation with a high level of accuracy. This strategy is of particular benefit for infiltrative pancreatic tumors which are poorly defined on CT-based imaging alone.

Published contouring atlases and consensus panel guidelines for target volume delineation have also helped to standardize radiation for pancreatic cancer, particularly in the postoperative setting. The contouring atlas for RTOG 0848 is still often references for delineating postoperative volumes [51].

Internal Motion Management

Internal motion can come from distension and peristalsis of luminal GI organs, but mostly comes from movement of the diaphragm with respiration. Such movement must be accounted for in treatment planning. Historically, this was achieved by using generous margins at the expense of an increased volume of normal tissue exposed to radiation. However, technologies in motion management have allowed for a higher level of certainty when delivering focal radiation to smaller field sizes in the treatment of pancreatic cancer.

The volume and position of luminal GI organs can change dramatically due to daily variations in contents. When treating tumors of the pancreas, consistent pre-treatment fasting for a specified number of hours can help ensure a stable gastric and duodenal volume throughout the duration of treatment. This is particularly important when treating with either high doses per fraction or tight margins. A low-residue diet is often recommended to minimize colonic gas, and regular bowel movements are encouraged at the same time with respect to treatment.

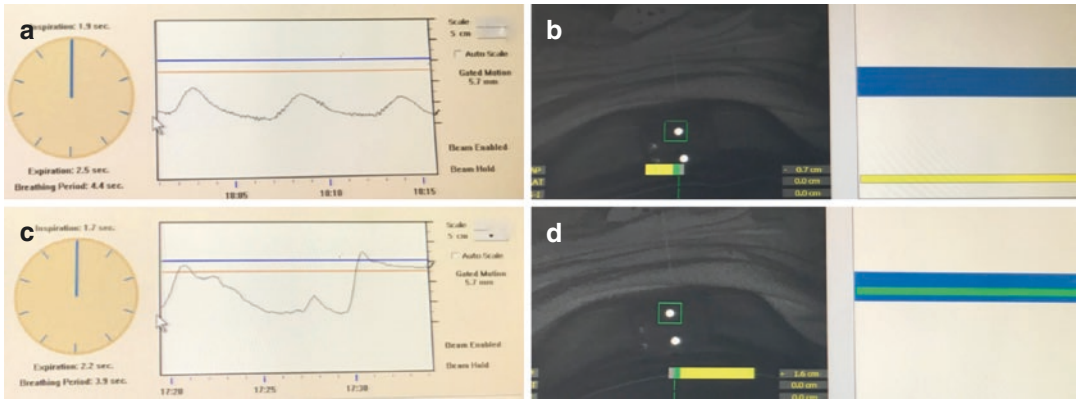

Fig. 13.2 This figure shows an example of visual feedback active breathing control using the Varian RPM system. A breathing motion detector is placed on the patient's abdomen. Motion during normal respiration is shown in (**a**). The patient is instructed to take a comfortable breath in and hold within a 5 mm window. Therapists are able to see when the patient holds their breath in the correct window (**b**). Goggles are worn by the patient which shows their breath represented by a line. The goal area for breath hold is represented by a blue bar (**c**), which is custom set based on the patient's normal respiratory amplitude and their ability to comfortably hold their breath during practice. When the patient holds their breath within the goal area, the yellow line turns green (**d**)

Pancreatic tumors can move substantially during the respiratory cycle due to their proximity to the diaphragm. There are several ways to quantify and plan for internal motion due to respiration. Four-dimensional CT (4DCT)-simulation is the use of multi-phase CT-simulation conducted throughout the different points in the respiratory cycle and allows for more accurate expansion of target volumes to account for demonstrated patient-specific respiratory motion. This can be done with or without IV contrast for better target delineation [52]. Two well-validated strategies in respiratory motion management include (1) motion compensating and (2) motion control. Motion compensating techniques (such as gating and tumor tracking) allow for free motion and only treat when motion is within certain parameters [53]. Tumor gating involves the use of reflective markers mounted on the abdominal skin surface, which are, in turn, monitored using camera systems. Tumor tracking is a similar concept, except with radio-opaque markers placed intra- or para-tumorally and monitored using fluoroscopic real-time imaging [54, 55]. Motion control techniques such as abdominal compression and active breath control decrease internal motion [56]. Active breath control uses a feedback system where the patient is able to monitor the variability of their breathing and thereby auto-regulate (Fig. 13.2).

Even with these interventions, there can still be substantial variation, so optimal daily image guidance is of the upmost importance [57]. Uncertainties in motion management may have even more profound implications in the delivery of particle radiation therapy [58]. The ideal motion management technique should take into account both tumor motion and daily variations in adjacent normal tissue anatomy.

Image-Guided Radiation Therapy

As radiotherapy spans multiple treatments over several days to weeks, daily localization of the pancreatic tumor and relevant surrounding normal anatomy is necessary to ensure dose delivery as planned. Most commonly, X-ray based imaging is used to match the bony anatomy each day with that on the reference imaging from the treatment planning simulation scan. This approach requires the assumption that the tumor target will not move with respect to the bony anatomy, or that the inter- or intra-fraction motion with

respect to the bony anatomy can be accounted for with adequate margins. With standard perioperative target volumes and doses, this is sufficient. For example, in the postoperative setting, a dose of 50.4 Gy in 28 fractions is delivered to a large volume to include the tumor bed, select anastomoses, surgical clips, and draining nodal basins at risk. For such a volume, daily X-ray based image guidance is appropriate because the postoperative fields are large and encompass nodal areas that do not move significantly with respect to the vertebral column.

For the pancreas itself, which can move with respect to the vertebral bodies, the accuracy of X-ray based daily image guidance can be improved with radiopaque fiducial markers in or adjacent to the tumor target. Gold fiducials are commonly placed for this purpose (Fig. 13.3). Although bile duct stents can be typically seen on plain film, they have not been shown to be a reliable or stable surrogate for hepatobiliary or pancreatic tumor position [59].

On-table cone-beam CT (CBCT) and CT on rails (CTOR) allow for CT imaging to be obtained at the time of treatment to ensure accurate and reproducible setup with respect to soft-tissue structures. This also allows for soft tissue matching to the tumor itself rather than relying on osseous structures alone. Shifts can also be made away from dose-limiting luminal GI structures should their position or distention vary from day to day. Finally, daily evaluation of patient habitus and anatomic relationships can help determine appropriateness for adaptive planning if treatment setup and margins no longer accurately cover the target and there is concern of exceeding normal tissue dose constraints.

MR-Linac

While most forms of adaptive radiotherapy use re-simulation and re-planning, techniques involving the real-time adaptive dose are being developed, especially in combination with MRI-based image guidance. MRI-based image guidance is currently being studied and holds particular utility in gastrointestinal malignancies, as these are often soft-tissue based. MRI-guided radiotherapy has been in clinical practice for several years and its utility in achieving excellent local control with SBRT for liver lesions has been reported in a recent multiinstitutional trial [60]. Given the difficulty with visualizing some pancreatic tumors on CT imaging, particularly without contrast, MR-guidance during radiation gives a higher degree of certainty that the correct target is treated and allows for the use of smaller margins. The daily variation of bowel contents and position can be accounted for and adaptive plans created based on the daily position of both tumor and normal tissues [61].

Bohoudi and colleagues from Amsterdam University described outcomes from 36 consecutive patients treated with MR-guided radiotherapy to 40 Gy in 5 fractions. They found online adaptation of plans was needed in approximately 53% of fractions delivered in order to either

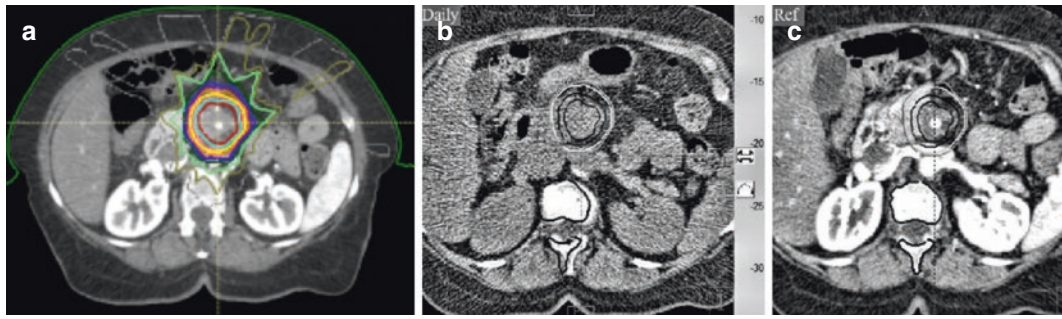

Fig. 13.3 This figure shows an example of a stereotactic body radiotherapy (SBRT) plan to 40 Gy in 5 fractions. Gold fiducials were placed endoscopically at least 24–48 h prior to simulation (**a**). At the treatment machine, the treating physician is able to compare the daily CT-on-rails images (**b**) with the reference images from the treatment plan (**c**). Fiducials are used for alignment, but daily CT-on-rails imaging is used to verify the position of surrounding normal tissues. Note the difference in the position of the stomach on panels (**b**, **c**)

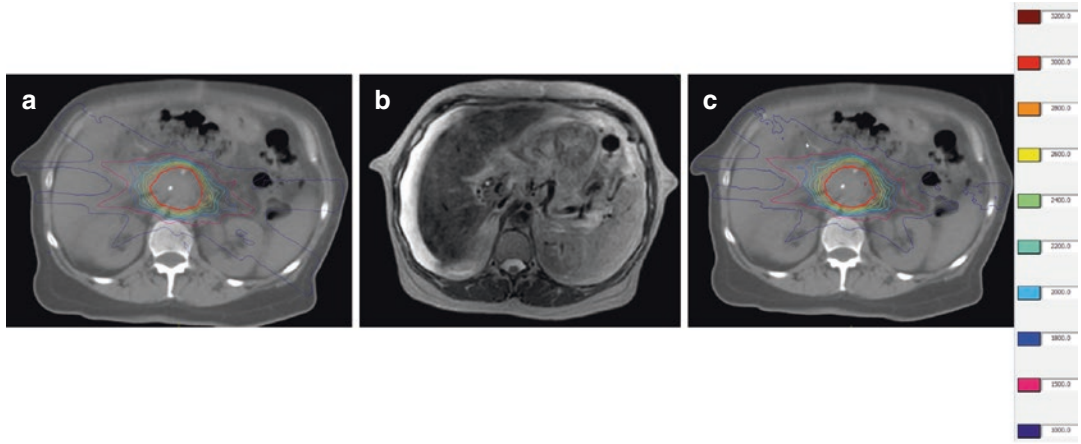

Fig. 13.4 This figure the radiation treatment plan (**a**), the daily MRI imaging (**b**) and the resultant adaptive plan using an adapt-to-position approach to create the adaptive plan by shifting the planning iso based on the fusion of planning CT and the daily MRI scan (**c**) for a patient with recurrent pancreatic cancer after prior surgery and radiation therapy. In the reirradiation setting, the dose prescribed was 25 Gy in 5 fractions

improve tumor coverage or decrease dose to organs at risk. Plans in which the tumor was either large and/or located ≤3 mm from an organ at risk were more likely to require real-time adaptation based on daily MR-guidance [62, 63]. Dr. Rudra and colleagues published a more heterogeneous series of patients treated with standard fractionation, hypofraction, and SBRT for pancreatic cancer using adaptive MR-guided radiation therapy [64]. In their series, MR-guidance and daily adaptation allowed for dose escalation to a BED of 70 or above in 24 (55%). Although high-BED radiation treatments required more frequent adaptation (83% vs 15%), the 2-year OS was significantly higher in the high-BED group (49% vs 30%; $P = 0.03$) [64]. Figure 13.4 shows an example of daily image guidance and daily online adaptive planning for a patient with pancreatic cancer.

Innovations in Radiation Techniques

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is currently indicated for preoperative, postoperative, or definitive treatment of pancreatic cancer in cases where normal tissue dose constraints cannot be achieved with 3D conformal techniques [2]. While traditional techniques required the adjustment of beam angles and physical blocks to shape dose distribution, IMRT utilizes "inverse planning" and dose optimization. Dose constraints and goals are designated to each individual structure, then treatment-planning software determines the optimal dose distribution that spares the most normal tissue while maximizing dose delivery to the target. A customized plan using multiple small beamlets angled at different positions around the patient allows for increased conformality.

IMRT has been widely adopted for the treatment of upper GI tract malignancies. Specifically for pancreatic cancer, IMRT has clear dosimetric advantages which can translate into toxicity reduction. Yovino and colleagues showed that patients receiving IMRT-based chemoradiation for pancreatic cancer had a lower overall incidence of G3-4 acute GI toxicities compared with those treated with 3D conformal radiation [65]. In addition to decreasing toxicities and improving patient quality of life, IMRT allows for simultaneous integrated boost technique, which can dose-escalate to higher-risk volumes without increasing number of treatments required [45].

Colbert and colleagues showed patients treated with dose-escalated radiation (63 Gy in 28 fractions, 67.5 Gy in 15 fractions, or 70 Gy in 28 fractions) using IMRT actually had significantly lower rates of G3 acute GI toxicity compared with patients who received standard dose radiation using 3D conformal techniques [66]. Figure 13.5 shows comparison plans for 50.4 Gy in 28 fractions delivered with IMRT versus 3D conformal techniques.

SBRT

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative body radiotherapy (SABR), is typically defined as a regimen consisting of five or fewer fractions delivering ablative doses and using advanced daily image guidance to achieve highly conformal margins. SBRT requires physician expertise but is also highly dependent on physics support due to the need for an extremely high level of setup reproducibility given the tight margins used. This technique offers the potential to increase the therapeutic ratio for pancreas-directed radiotherapy because the increased biologically effective dose delivered improves the chances for local control, and the decreased dose to adjacent normal tissues reduces the toxicity. There are additional logistical benefits of SBRT, particularly patient convenience and decreased time without systemic therapy. SBRT has been integrated into the multidisciplinary management of both borderline resectable and locally advanced pancreatic cancer, although recent consensus guidelines suggest low quality of current evidence and a conditional strength of recommendation to use SBRT either in the preoperative or definitive settings [67].

For borderline resectable pancreatic cancer, the goal of preoperative SBRT is the same as any multidisciplinary neoadjuvant regimen to increase the chances of an R0 resection and improve local control. Retrospective studies from Moffitt Cancer Center described the use of SBRT after initial chemotherapy. The regimen included 25–30 Gy to the tumor with an additional boost

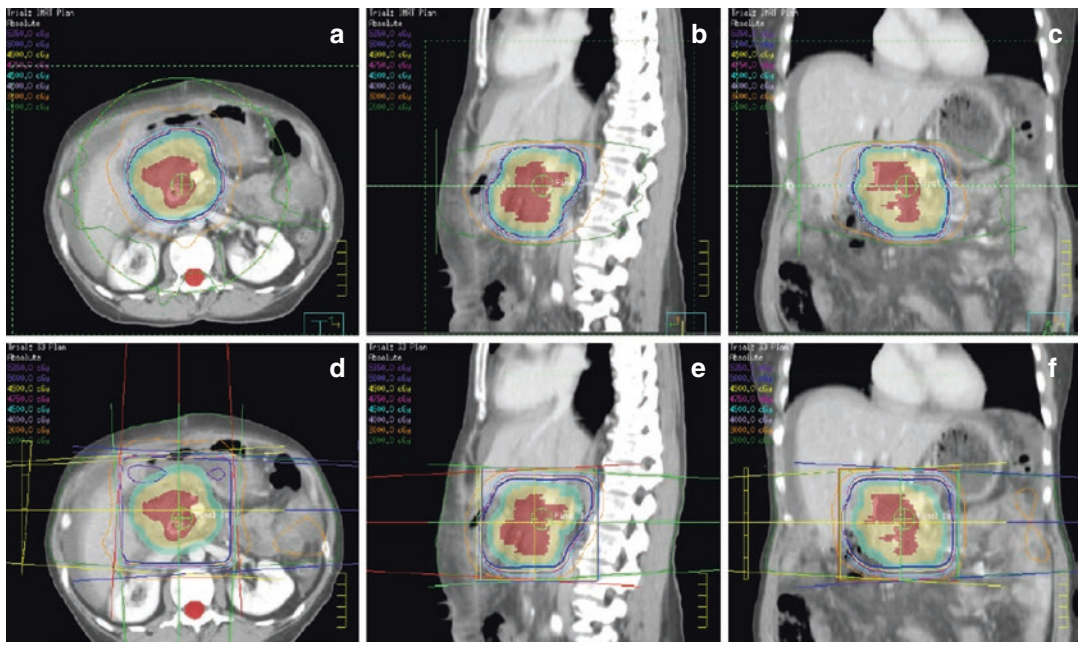

Fig. 13.5 This figure shows axial (**a**, **d**), sagittal (**b**, **e**), and coronal (**c**, **f**) from a comparison plan comparing 3D conformal radiation technique (**d**–**f**) and intensity-modulated radiation therapy (IMRT) technique (**a**–**c**) for a patient receiving preoperative chemoradiation to 50 Gy in 25 fractions

to the tumor vessel interface. Of 73 patients treated with this regimen at Moffitt, 56% went on to have surgery, and 97% of those had negative margins. Late G3 toxicities were very low at approximately 5% [68, 69]. There was initial concern that the increased dose per fraction and overall compressed time course of SBRT may lead to increased operative complications, but retrospective reports from Johns Hopkins were reassuring against this [70]. Despite encouraging early data, some concerns emerged regarding the smaller volumes used for SBRT leading to a high risk for compromised local control. Marginal local failure rates were reported for patients treated on a phase II trial of neoadjuvant chemotherapy followed by SBRT for resectable and borderline pancreatic cancer. In this group of 15 patients with borderline disease, the rate of local failure was 50%, and all local failures were outside the 33 Gy planning target volume which would have been covered with traditional chemoradiation [71]. Interestingly, in the locally advanced setting, most studies have reported high rates of local control with SBRT (see below); however, this patient population generally has a worse prognosis than borderline resectable patients resulting in less time to identify local failures. Results from ongoing and recently completed studies are needed to further describe the safety and efficacy of SBRT in the setting of multidisciplinary neoadjuvant treatment; SRPCNCC-1 and ALLIANCE A021501 are two examples asking this question [34, 72]. The radiation planning guidelines for A021501 include requirement of fiducial placement prior to simulation for treatment planning. Motion management is required either with a 4D CT scan to show tumor position in all phases of the respiratory cycle or with breath-hold scans. The largest volume (PTV1) receives 25 Gy in 5 fractions and includes the gross tumor volume plus the tumor vessel interface with a 3 mm volumetric expansion. The intermediate volume (PTV2) starts with PTV1 and subtracts out a volume consisting of the adjacent bowel structures (PRVgi) plus 3 mm. This volume receives 33 Gy in 5 fractions. The smallest volume (PTV3) consists of the tumor vessel interface plus 3 mm and then subtracts out the PRVgi. This volume receives the highest dose of 36 Gy in 5 fractions. Dose constraints to normal tissue include keeping the volume of duodenum, small bowel, and stomach receiving 35 Gy to 1 cc or less.

Compared with the neoadjuvant literature, there have been more studies describing outcomes and toxicities for the use of SBRT for patients with locally advanced pancreatic adenocarcinoma. It gained popularity in some centers due to its potential to deliver dose-escalated radiation for the purposes of definitive local control and/or palliation without delaying chemotherapy, and it is listed in current NCCN guidelines for select patients [2]. Both single- and multi-fraction SBRT schedules have been studied with multifraction SBRT boosting lower rates of GI toxicity without reduced local control [73]. One study established the optimum timing for SBRT in the setting of locally advanced pancreatic cancer to be after initial chemotherapy in order to select out patients who will not develop early metastases [74]. A systematic review of 19 studies including 1009 patients was performed and pooled results showed a one-year OS of 52% with a median OS of 17 months. Locoregional control at 1 year was 72%, and local control appeared to correlate with total SBRT dose and number of fractions [75]. A more recent meta-analysis of 15 studies across 12 institutions showed the most common SBRT regimen for patients with locally advanced pancreatic cancer was 30 Gy in 5 fractions, though the range was large. Overall, the one-year LC rates ranged from 60 to 83% with G3+ toxicity <7% across all studies [76]. It has been recognized that standardization of dose and fractionation is needed before initiating randomized trials in this space. To this end, the Australasian Gastrointestinal Trials Group (AGITG) and the Trans-Tasman Radiation Oncology Group (TROG) published joint guidelines on pancreas SBRT which promoted 40 Gy in 5 fractions as the recommended dose and treatment were delivered during end-expiratory breath hold with triple-phase contrast enhanced CT used for image guidance [77]. There are ongoing randomized trials in this space including one randomizing patients with locally advanced

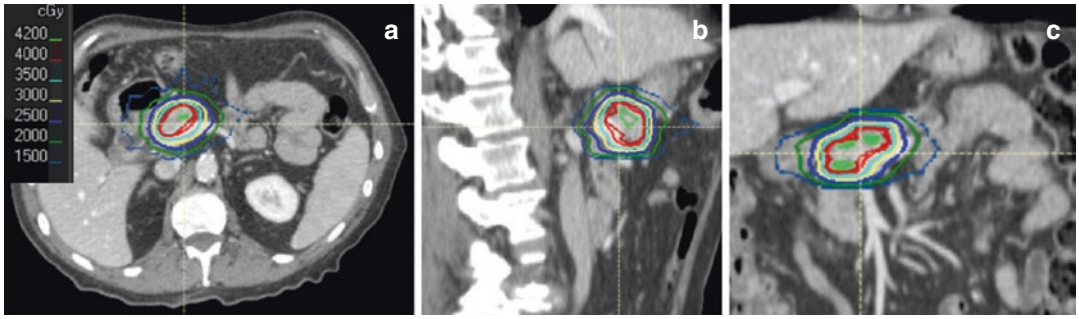

Fig. 13.6 This figure shows representative axial (**a**), sagittal (**b**), and coronal (**c**) images for the radiation plan for a patient with medically inoperable adenocarcinoma of the head of the pancreas treated definitively to a total dose of 40 Gy in 5 fractions. Note that the duodenum was adjacent to the gross tumor volume but there was no duodenal invasion

pancreatic cancer to modified FOLFIRINOX chemotherapy with or without SBRT to 40 Gy in 5 fractions [78] (Fig. 13.6).

Particle Beam Radiation

Early proton planning studies first showed the potential benefits of proton beam radiation in the treatment pancreatic cancer by decreasing unnecessary dose to the abdominal organs particularly when tumors required large treatment fields [79]. Other treatment planning studies also demonstrated the benefits of proton beam radiation in reducing low to moderate doses to normal tissues including the spinal cord, kidneys, liver, stomach, and small bowel [80, 81]. Two studies showed that proton beam radiation could be used to safely dose-escalate while still reducing mean doses to the surrounding organs at risk [81, 82]. However, there are concerns regarding the robustness of proton plans in the treatment of pancreatic cancer. One study showed that proton plans were highly susceptible to interfractional anatomic changes. The coverage of the clinical target volume could be reduced by 8% as a result of the daily variability [83]. Figure 13.7 shows IMRT and IMPT comparison plans for patient treated with SBRT for borderline resectable pancreatic cancer in the neoadjuvant setting.

The University of Florida group first treated a heterogeneous group of patients with pancreatic and periampullary tumors with standard fractionation proton beam therapy to a total dose of 50.4–59.4 Gy relative biologic effectiveness (RBE) [84]. Five patients were treated postoperatively, and 17 were treated upfront: five patients deemed to have borderline resectable disease and 12 deemed to have locally advanced disease. No patient experienced G3+ toxicity, and patients in whom anterior and left lateral fields were omitted did not experience G2 toxicity [84].

Hong and colleagues conducted a phase I study at Massachusetts General Hospital which evaluated four dose levels of neoadjuvant proton beam radiation tested in patients with localized, resectable adenocarcinoma of the head of the pancreas [85]. The proton regimens ranged from 3Gy(RBE) × 10 fractions (dose level 1) to 5 Gy (RBE) × 5 fractions over 1 week (dose level 4), and 5 Gy (RBE) × 5 fractions was established as the maximum tolerated dose (MTD). Concurrent capecitabine was given, and patients underwent surgery 4–6 weeks after completion of proton radiation. Of the 15 patients enrolled, four had G3 toxicities (pain, biliary stent obstruction, and infection), and 11 (73%) went on to undergo surgical resection. There were no unexpected postoperative complications, which was an important finding for the use of a new preoperative modality in a disease where surgery offers the definitive treatment [85]. These results prompted a subsequent phase II study on which 35 additional patients were enrolled and treated

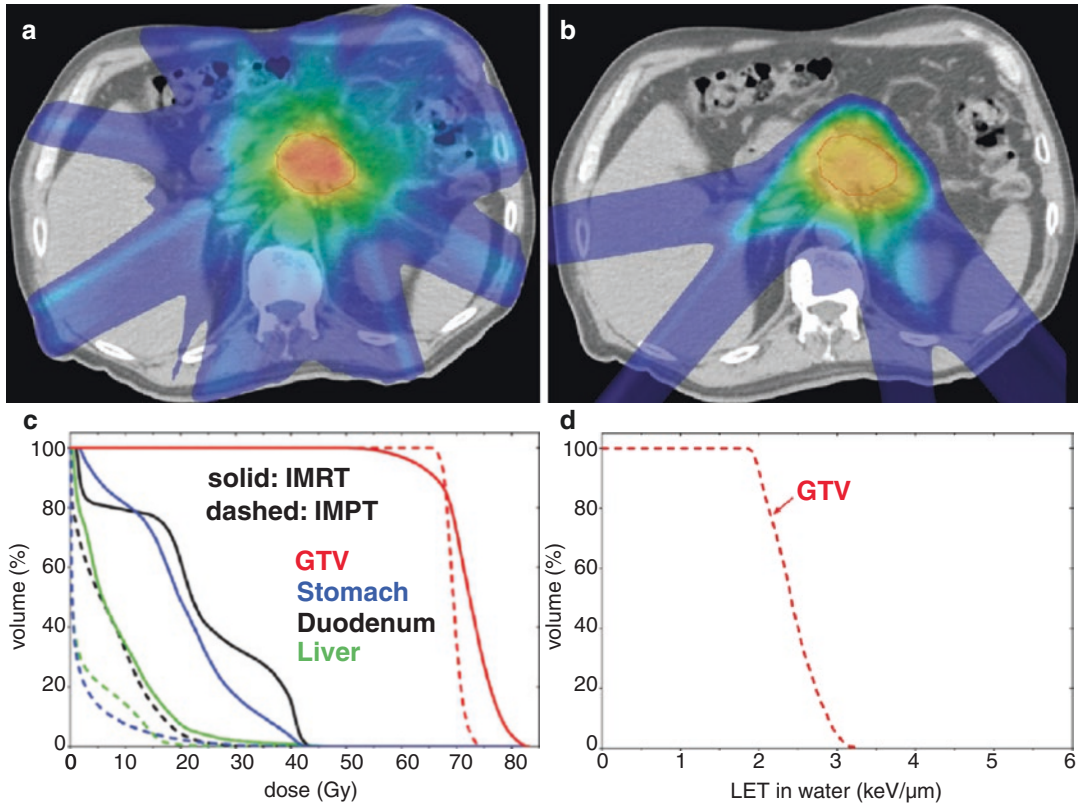

Fig. 13.7 This figure shows representative axial images for an intensity-modulated radiation therapy (IMRT) plan (**a**) compared with an intensity-modulated proton therapy (IMPT) plan (**b**) for a patient with unresectable adenocarcinoma cancer in the body of the pancreas. The prescription dose is 67.5 Gy in 15 fractions. Panel (**c**) shows the dose volume histogram with IMRT represented by the solid lines and IMPT represented by the dashed lines. Panel (**d**) shows the percentage of the gross tumor volume and corresponding linear energy transfer (LET)

with the established MTD of 5 Gy (RBE) × 5 fractions [86]. The treatment had a low acute G3 toxicity rate at 4.1%. The median PFS was 10 months and the median OS was 17 months. Locoregional failure occurred in 16.2% of patients and distant failure was the predominant pattern of failure at 72.9%. These LC and OS results are slightly better than those reported in photon-based SBRT series (median survival of 14.5 months and 1 year LC of 61%), but this is likely related to patient selection and randomized clinical studies are still needed to compare the two modalities [87].

Proton beam radiation has an even greater potential to advance treatment for patients with inoperable pancreatic cancer who have no standard curative options. Terashima and colleagues conducted a phase I/II study at the Hyogo Ion Beam Medical Center in which 50 patients with locally advanced pancreatic cancer were treated with gemcitabine-based chemoradiation. Five patients with tumors adjacent to GI organs received 50 Gy (RBE) in 25 fractions, but the other 45 received moderate hypofractionation (70.2 Gy (RBE) in 26 fractions or 67.5 Gy (RBE) in 25 fractions). The efficacy of this regimen was encouraging with a one-year freedom from local progression and OS of 81.7% and 76.8%, respectively. However, 12% of patients were not able to complete treatment as planned due to acute hematologic or GI toxicities [88]. Additionally, a follow-up publication outlining GI toxicity for patients on this study showed that nearly 50% had radiation-induced ulcers in the stomach or duodenum, though only 10% had clinical symptoms or bleeding [89]. It is unclear what degree

of toxicity was caused by the dose escalation, the concurrent gemcitabine, or uncertainties related to proton beam planning and delivery at the time.

Newer proton therapy techniques such as intensity-modulated proton therapy (IMPT) have been studied by Jethwa and colleagues from the Mayo Clinic. When giving 50 Gy (RBE) in 25 fractions with concurrent capecitabine or 5-fluorouracil, there were no G3+ GI toxicities and no changes to baseline patient reported outcomes [90]. Dose escalation using proton therapy should still be attempted with caution, and more data about linear energy transfer (LET) distribution and its clinical significance may help improve safety of this approach [91].

Carbon ion beam therapy has physical and biologic characteristics which can offer an even more conformal dose distribution around the tumor target. It may offer better tumor control because of increased linear energy transfer compared with both X-rays and protons.

The first clinical study to evaluate the efficacy and safety of carbon ion therapy for locally advanced pancreatic cancer was performed in Japan and included 72 patients treated at three Japanese carbon beam facilities [92]. A hypofractionated course was used with a dose of either 52.8 Gy (RBE) or 55.2 Gy (RBE) in 12 fractions. Seventy-eight percent of patients received concurrent chemotherapy. Oncologic outcomes were encouraging, including median OS of 21.5 months and 2-year cumulative local recurrence rate of 24%. Twenty-six percent of patients developed acute G3-4 hematologic toxicities, 3% developed G3 anorexia, and late G3 GI toxicity was only seen in one patient. Median survival rates were better than patients receiving chemotherapy alone (16.5 months) and standard chemoradiation (15.2 months) on the LAP07 trial [16]. However, these results were far from curative. Additionally, the majority of patients in this study had tumors in the body or tail of the pancreas because patients with tumors immediately adjacent to the gastrointestinal tract (<1 mm) were excluded from carbon ion therapy. With this careful patient selection GI toxicity rates were quite low compared to SBRT and proton series with similar dose escalation.

A recently published phase I dose escalation trial evaluated combination proton and carbon ion therapy for patients with locally advanced pancreatic cancer. The proton component was 50.4 Gy (RBE) in 28 fractions with escalated doses of carbon ion therapy given as a boost ranging from 12 Gy (RBE) to 18 Gy (RBE) in 3 Gy (RBE) fractions. There were no dose-limiting toxicities (described as G3+ nonhematologic toxicity), but G1-2 GI and hepatic toxicities occurred in 40% of patients. However, no significant difference in local control or OS was observed with increasing boost dose with these small numbers [93].

Carbon ions are subject to some of the same sensitivities to daily anatomic changes within the abdomen that affect protons [83]. A worst-case optimization strategy, which has been studied in carbon ion therapy for pancreatic cancer, may be useful to mitigate risks posed by interfractional anatomic changes [94].

Conclusions

Recent advances in radiation therapy planning and delivery have served to improve the therapeutic ratio for patients with pancreatic cancer. Advances in imaging, motion management, and image guidance have allowed for tighter margins and smaller target volumes with less exposure to non-target normal tissues. More conformal techniques such as stereotactic body radiation therapy and particle therapy can allow for a more favorable dose distribution. These advances may continue to expand the role of radiation in the multidisciplinary treatment of pancreatic cancer.

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Part IV

Endoscopic Management of Pancreatic Cancer Symptoms

14 Jaundice/Biliary Obstruction: ERCP/EUS BD

Seifeldin Hakim and William A. Ross

Introduction

Approximately one in eight pancreatic cancer patients will present with jaundice and half will develop jaundice at some point in their disease process [1, 2]. Jaundice as a presenting symptom is associated with a shorter interval of time between symptom onset and diagnosis as well as between initial presentation and diagnosis [1]. As a symptom that prompts patients to seek care and results in expedited evaluations, the tendency for jaundice to occur with pancreatic head lesions may account for the modest survival advantage over body or tail cancers [3]. For patients presenting with jaundice and suspected to have pancreatic pathology, a pancreatic protocol computed tomographic study is recommended as an initial imaging study [4]. If the jaundice is found to be from an obstructing pancreatic lesion, both endoscopic retrograde cholangiopancreatography (ERCP) for decompression and endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) for diagnosis and sometimes staging can be readily performed in one session [5].

For patients with known pancreatic mass or cancer, the need for biliary decompression is straight-forward in those presenting with cholangitis or unresectable disease for either therapeutic or palliative purposes [6]. However, in rare patients when upfront resection is contemplated, the role of pre-operative biliary decompression remains an area of long-standing controversy. As the literature stands currently, there is no evidence to support routine pre-operative drainage [7]. The frequency of such drainage has increased dramatically over the years despite previous reports on increased post-operative complications in patients who had pre-operative biliary drainage [8, 9]. Some argue that decompression should be performed in cases of severe hyperbilirubinemia with total bilirubin of 7.5 mg/dl or higher [10]. Also, there is a preference for early biliary decompression in patients with potentially resectable disease in whom neoadjuvant treatment is planned in anticipation of curative surgical resection. Early biliary decompression in these patients will minimize interruptions in the neoadjuvant therapy [11–14].

Options for Biliary Decompression

If decompression is desired, the options range through surgery, percutaneous to endoscopic. Early randomized trials showed endoscopic stenting to be: (1) superior to surgical biliary bypass in terms of procedure-related mortality, morbidity, and mean hospital stay and (2) supe-

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_14

rior to percutaneous drainage in terms of relief of jaundice, quality of life, morbidity, and 30-day mortality [15, 16]. Longer term concerns about possible tumor seeding from percutaneously placed stents have been borne out adding more evidence that endoscopy is the preferred modality [17].

In general, there are three types of stents that can be used for biliary decompression due to malignant stricture during ERCP, which are: (1) plastic stent (PS), (2) covered self-expandable metal stent (CSEMS), and (3) uncovered self-expandable metal stent (USEMS) (Fig. 14.1). There is no optimal stent type to be used in malignant biliary strictures and choice depends on the therapeutic gastroenterologist's preference and the expected survival time. However, recent data has shown advantages with self-expandable metal stents (SEMS) whether covered or uncovered over PSs in malignant biliary obstruction [18, 19]. A European meta-analysis showed that the rate of endoscopic re-intervention prior to surgery and post-operative pancreatic fistula was statistically significantly lower in SEMS group compared to PS group but this study was limited only to those with resectable pancreatic head tumors. Sawas and colleagues [20] showed that SEMS are superior to PS in terms of patency at 4 months. Almadi et al. [19] showed in a series of meta-analyses for palliation of malignant biliary obstruction that SEMS use is associated with longer stent patency, lower complication rates, and fewer re-interventions when compared to PS (Figs. 14.2 and 14.3). Randomized trials have failed to demonstrate overall advantage of CSEMS over USEMS. Both CSEMS and USEMS have comparable stent patency and overall adverse effects with similar patient survival time. CSEMS tends to have higher rate of stent migration, tumor overgrowth, and cholecystitis when compared to USEMS. However, USEMS tends to have higher rate of tumor ingrowth when compared to CSEMS [21–24]. In addition, trials have shown no cost advantage to PS vs SEMS and no cost advantage to USEMS vs CSEMS [25] (Figs. 14.4 and 14.5).

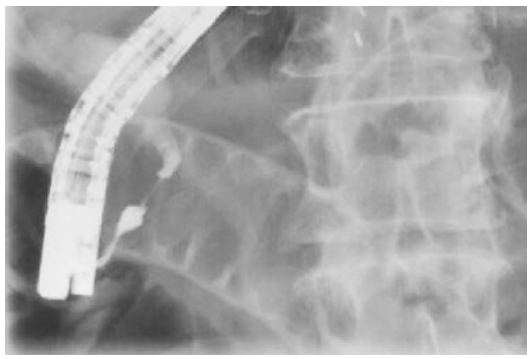

Fig. 14.1 Fluoroscopic view showing malignant stricture of distal common bile duct

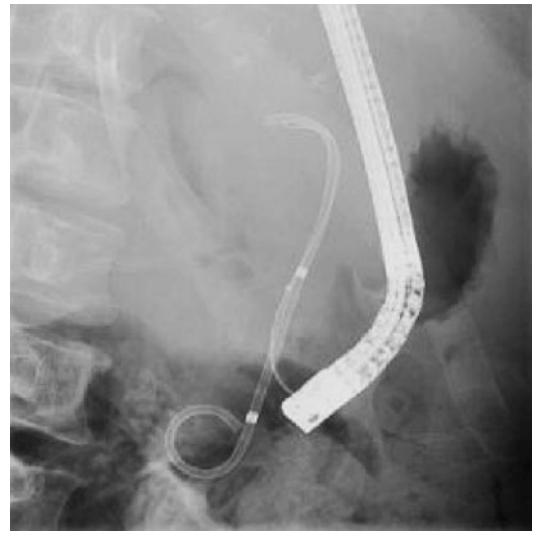

Fig. 14.2 Fluoroscopic view showing plastic stent in the biliary tree

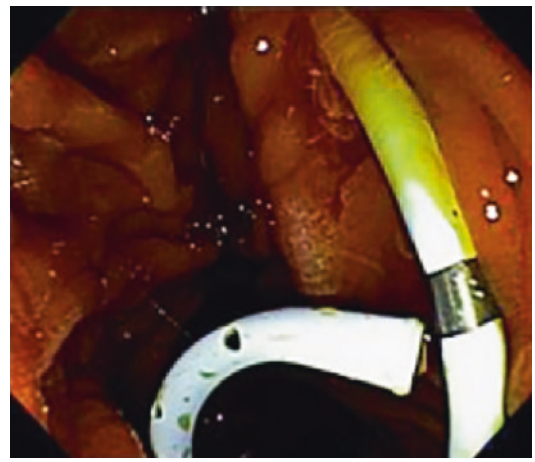

Fig. 14.3 Endoscopic view of plastic biliary stent

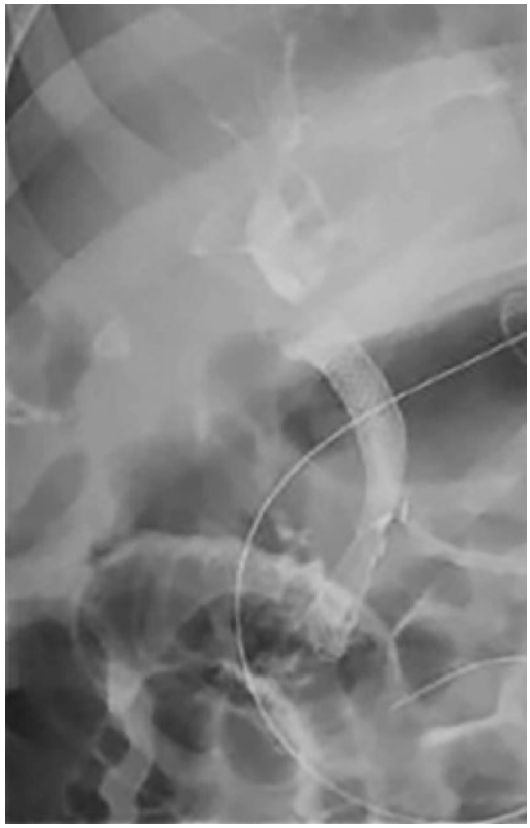

Fig. 14.4 Fluoroscopic view showing metal biliary stent placed in the common bile duct

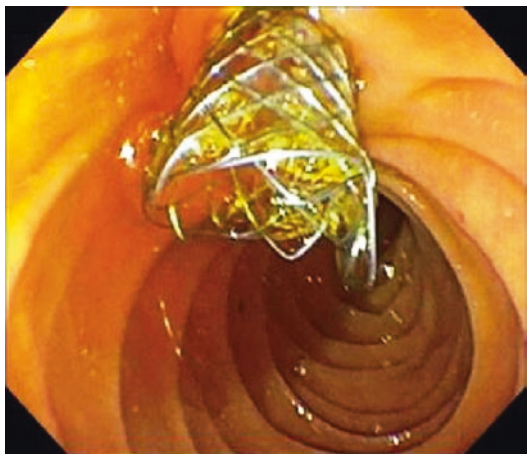

Fig. 14.5 Endoscopic view of metal biliary stent

Metastatic hilar adenopathy in patients with body and tail cancers can lead to hilar strictures. Again, multiple approaches can be considered with endoscopic and percutaneous approaches having their own advocates [14, 26]. Whatever approach is chosen, USEMS placement tends to be the preferred stent type. Cross-sectional imaging should guide stent placement to focus on drainage of 50% or more of liver volume in those with decompensated liver function, and 33% or more in those with normal or compensated liver function [27, 28]. Planning biliary stent placement should take into consideration the avoidance of atrophic segments as instrumentation will have little benefit and only increased risk of cholangitis [28, 29]. Opacification should be limited only to ducts that can be stented [30]. The benefits of bilateral drainage over unilateral stenting are debated but if technically possible, bilateral drainage should be considered [20, 31, 32].

However, endoscopic drainage is not always feasible and is unsuccessful in less than 10% of the cases likely due to altered anatomy from prior surgery (e.g. bariatric), duodenal obstruction from the pancreatic cancer or from a previously placed duodenal stent. In such cases, alternative approaches such as percutaneous transhepatic biliary drainage (PTBD) or EUS-guided biliary drainage (EUS-BD) can be considered [33].

PTBD has a high clinical success up to 97% but it has its own drawbacks due to the relatively high morbidity and mortality and its impact on patient quality of life [34]. It has been reported that PTBD has a relatively high procedure-related morbidity up to 33%, which includes: bleeding, cholangitis, sepsis, acute pancreatitis, biloma formation, bile leak, biliovenous fistula, pneumothorax, peritonitis, or perforation. Also, it has been reported that PTBD related-mortality can be up to 6% [34]. The presence of biliary dilation makes a difference as patients with non-dilated intrahepatic bile ducts have 14.5% PTBD procedure-related morbidity compared to 7% in patients with dilated intrahepatic bile ducts [33–35]. Another shortcoming for PTBD use is the catheter-related complication that can happen after successful placement of the drainage catheter. Nennstiek and colleagues [35] showed in a 10-year analysis that about 40% of patients with PTBD requiring long term frequent exchanges suffered from catheter-related complications or

problems at some point. These complications included pain at the catheter site, catheter occlusion, dislocation, or cholangitis.

EUS-guided biliary drainage (EUS-BD) is an evolving technique that started to gain popularity in the last few years for obtaining biliary access after unsuccessful ERCP. EUS-BD has some advantages over PTBD, which has been the more traditional alternative to ERCP. These advantages are the minimally invasive nature of the procedure with little to no procedural pain, it can be performed in the same setting after failed ERCP by the same therapeutic gastroenterologist, no external drain is required, a lower rate of adverse events, and offers a relatively better quality of life than PTBD [33, 36, 37].

Different EUS-BD techniques have been introduced over the last few years to help to achieve biliary decompression after failed ERCP. EUS-BD approaches include EUS-rendezvous technique with transpapillary stent placement and EUS-BD with antegrade stent placement. Data so far argues that there are fewer complications with the rendezvous technique [38, 39]. Antegrade EUS-BD transluminal approaches include EUS-guided choledochoduodenostomy and EUS-guided hepaticogastrostomy [33, 36, 38, 40]. Lee et al. [36] showed in their prospective randomized multicenter controlled clinical trial in South Korea ($N = 66$) that transluminal EUS-BD has similar technical and clinical success but lower adverse events and re-intervention rate when compared to PTBD group. The same results were shown in a meta-analysis that included 8 additional studies [41]. Multiple meta-analyses showed similar technical and clinical success and similar adverse event rate between EUS-BD and ERCP for malignant biliary obstruction [42, 43]. Yet these are early reports on EUS-BD that are subjected to publication bias and more data is needed to make any changes in initial approach to these patients. Published complication rates are high averaging 17–19% but rates are lower with metal stents compared to plastic stents. Complications are likely to be even lower with new stent designs readily adapted to this indication like luminal apposing metal stents (LAMS) [33].

Recently EUS-guided transmural gallbladder drainage such as cholecystoduodenostomy or cholecystogastrostomy has been introduced as other approaches for decompressing malignant biliary obstruction. Limited data is available for these techniques but it can be used as a salvage method only if cystic duct is patent and the previously mentioned measures fail to decompress malignant biliary obstruction until more data is available in the literature about the efficacy and safety [44, 45]. Drawbacks to EUS-BD are that it is still evolving and there is a need for more randomized controlled trials with the new stent designs that are being developed with this indication in mind. Also, this procedure is currently performed in large academic centers and its generalizability to the wider endoscopy community is to be determined.

In summary, biliary obstruction is common with pancreatic cancer. ERCP is the most commonly used technique for biliary decompression. Different types of biliary stents are available. Each stent type has its own pros and cons and there is no stent type of optimal choice for all pancreatic cancer patients but there is a tendency to prefer self-expandable metal stents over plastic stents. Selection mainly depends on case-by-case evaluation, provider preference, and resource availability. Percutaneous transhepatic biliary drainage as an alternative to ERCP has a high technical and clinical success but PTBD has its own drawbacks, which in part led to introduction of new alternative and promising techniques including EUS-BD. Endoscopic ultrasound guided biliary drainage is being used in different ways to facilitate biliary access and drainage when ERCP is unsuccessful and it may become the first modality after failed ERCP in the next few years.

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15 Gastric Outlet Obstruction: Antroduodenal Stenting, Venting PEG, EUS Guided Gastrojejunostomy

Phillip S. Ge and Christopher C. Thompson

Introduction

Malignant gastric outlet obstruction (mGOO) is a feared late complication of pancreatic cancer. From various studies, it is estimated that between 5 and 25% of patients with pancreatic cancer will ultimately develop mGOO [1, 2]. The onset of mGOO portends a poor prognosis, with historical series demonstrating a median survival of 3–4 months [3, 4]. The presentation of mGOO is often indolent, however can range from acute to subclinical. A diagnosis can be made based on clinical, endoscopic, and/or radiographic findings. Although mGOO traditionally required surgical management, a modern, multidisciplinary approach involving minimally invasive endoscopic techniques is increasingly used. Here, we present an overview of the pathophysiology, diagnosis, and management of patients with mGOO.

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Pathophysiology

Malignant GOO can occur at various levels depending on the location of the primary pancreatic cancer (Table 15.1). mGOO occurring at the duodenal bulb and duodenal sweep occurs from cancers at the head of the pancreas. mGOO occurring at the periampullary second portion of the duodenum arises from cancers at the pancreatic uncinate process or periampullary portion of the pancreas. mGOO occurring in the distal duodenum typically arises from cancers at the body or tail of the pancreas or from bulky mesenteric lymphadenopathy. mGOO occurs at these vari-

Table 15.1 Pathophysiology of malignant gastric outlet obstruction

Location[a]	Etiology
Gastric outlet (antrum, pylorus)	Gastric cancer
First portion of duodenum (bulb, sweep)	Cancer of the head of the pancreas Cholangiocarcinoma
Second portion of duodenum (periampullary)	Cancer of the uncinate process of the pancreas Ampullary cancer
Third/fourth portion of duodenum	Cancer of the body or tail of the pancreas Bulky metastatic lymphadenopathy
Gastrojejunal anastomosis (post-Whipple)	Benign: tissue edema, anastomotic strictures Malignant: local recurrence

[a] Of note, duodenal cancer and metastatic cancer can present with obstruction at any of the levels noted above

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_15

ous locations from a combination of direct invasion of the pancreatic cancer into the duodenal wall and local edema of the duodenal wall due to mass effect from the adjacent malignancy.

In patients who have undergone either traditional or pylorus-preserving Whipple pancreaticoduodenectomy, gastric outlet obstruction can be either benign or malignant and tends to occur at the gastrojejunal anastomosis. Benign obstruction can arise due to strictures or localized tissue edema at the gastrojejunal anastomosis. Malignant obstruction is often due to local recurrence of pancreatic cancer.

Diagnosis

mGOO typically presents with the insidious onset of nausea, vomiting, anorexia, early satiety, and abdominal pain [5]. The emesis can often include undigested food products and can be malodorous. When prompted, patients routinely offer a history of worsening reflux symptoms and vomiting foodstuffs that are several days old. Owing to its insidious nature, patients rarely report significant drops in appetite and early satiety; although this is often observed by the patients' close relatives or loved ones. The presence of bile within the emesis can often result in a dark appearance that can be mistaken for coffee ground emesis and foregut bleeding.

mGOO is generally diagnosed radiographically with cross-sectional abdominal imaging such as computed tomography (CT), which may demonstrate a markedly distended stomach [6]. Occasionally, mGOO is diagnosed endoscopically, either during evaluation of nausea/vomiting or coffee ground emesis, or incidentally during attempted endosonography (EUS) and/or endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 15.1).

Patients with mGOO experience severely decreased quality of life due to symptoms such as nausea, vomiting, abdominal pain, and nutritional deficiencies which are often exacerbated by the effects of the primary pancreatic malignancy. The nutritional deficiencies that accompany mGOO likely contribute to the poor prognosis of pancreatic cancer once mGOO has developed. However, given the proportion of patients with subclinical symptoms, the incidence of undiagnosed mGOO in pancreatic cancer is likely underestimated as patients and relatives may attribute the symptoms to that of systemic chemotherapy or to progressive decline from the primary pancreatic cancer.

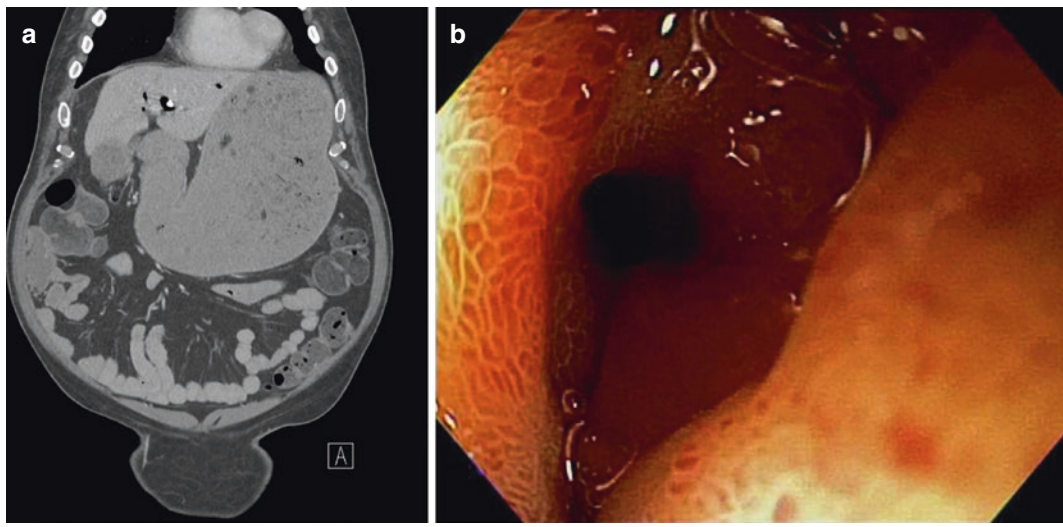

Fig. 15.1 Malignant gastric outlet obstruction. (**a**) Radiographic appearance of a typical patient with gastric outlet obstruction due to pancreatic malignancy, as seen on coronal views on computed tomography. (**b**) Endoscopic appearance of a severe duodenal stricture due to adjacent malignancy at the head of the pancreas

Principles of Management

The principles of management for mGOO can be separated into three categories—maintaining luminal patency, luminal bypass, and decompression. Enteral stent placement using a self-expanding metal stent (SEMS) is commonly performed to maintain luminal patency. Luminal bypass has traditionally been achieved surgically, with either open or laparoscopic gastrojejunostomy. More recently, EUS-guided gastroenterostomy (EUS-GE) has emerged as a minimally invasive alternative to achieve luminal bypass. Finally, in patients where luminal patency cannot be maintained and bypass is not an option, gastric decompression with placement of a venting gastrostomy tube can be performed as a last resort for palliation of mGOO.

Patients presenting with mGOO should be clinically optimized prior to proceeding with any procedure. The stomach should be fully decompressed using a large diameter nasogastric tube. During this time, intravenous fluids should be given to counteract the effects of volume depletion, and electrolyte abnormalities should be identified and corrected. In our practice, endoscopic procedures in the management of mGOO are performed under general endotracheal anesthesia, often with a rapid-sequence intubation, due to the risks of aspiration in the setting of obstruction. Parenteral antibiotics should be administered for patients undergoing surgical gastrojejunostomy, EUS-guided gastroenterostomy, and venting gastrostomy tube placement.

Surgical Gastrojejunostomy

Prior to the advent of enteral stent placement, the management of mGOO was limited to either surgical gastrojejunostomy or palliative venting gastrostomy. Today, laparoscopic surgical gastrojejunostomy remains an attractive option for patients who present with mGOO who have good performance status and a reasonable life expectancy [7, 8].

Open surgical gastrojejunostomy is traditionally performed using an upper midline or subcostal incision, and laparoscopic gastrojejunostomy is typically performed using several small incisions, to accommodate multiple 5-mm ports and one 12-mm port for the laparoscopic stapler [9, 10]. The greater omentum is dissected off the greater curvature of the stomach to expose the inferior and posterior surface of the stomach. A suitable loop of proximal jejunum is identified and brought to the stomach. An enterotomy is made into the loop of jejunum, followed by a gastrotomy along the posterior and most dependent portion of the stomach. A side-to-side antecolic or retrocolic gastrojejunostomy is then created using a surgical stapler, and the enterotomy closed either with the stapler or with sutures. If tumor ingrowth or extrinsic compression of the common bile duct is noted at the time of gastrojejunostomy, a "double bypass" with choledochojejunostomy or hepaticojejunostomy can be additionally performed.

Several modifications of laparoscopic gastrojejunostomy have been described. In a partial stomach-partitioning gastrojejunostomy, the stomach is partitioned vertically, allowing enteric contents to favorably empty inferiorly across the gastrojejunostomy rather than towards the native gastric outlet [11]. Another variation is known as the modified Devine exclusion with vertical stomach reconstruction [12]. In this technique, the stomach is vertically transected, then the proximal portion of the stomach is stretched and then resected horizontally with a stapler, akin to a wedge resection of the dependent portion of the stomach. A loop of jejunum is then brought up and anastomosed in a horizontal side-to-side fashion.

Surgical gastrojejunostomy has historically been the gold standard for the management of mGOO. However, surgery carries considerable risks of morbidity and mortality. Morbidity typically includes delayed gastric emptying and postoperative ileus; however, there are also less common but serious adverse events such as anastomotic leakage. Prior to widespread use of enteral stents, large surgical series showed that palliative gastrojejunostomy carried surgical morbidity and mortality rates of 39% and 31%, respectively, with median survival of 4 months

[13]. Variables associated with shorter survival rates included advanced disease stage and Karnofsky performance status score less than 80. Re-intervention was necessary in 16.6%, and 20% of patients were never able to tolerate a normal diet. These findings were reflected in several additional surgical series, which reported delayed gastric emptying and postoperative ileus to occur in up to 58% of patients [4, 14], and median procedure-related hospital stay ranging from 14 to 24 days [15, 16]. Given that surgical risks were found to be higher particularly among patients with poor performance status or limited life expectancy, more contemporary studies revisiting this issue have concluded that surgical gastrojejunostomy should be reserved for patients with good performance status and reasonable life expectancy [17, 18].

Table 15.2 Commercially available endoscopic stents in the USA

Company	Stent[a]	Available sizes
Boston Scientific	WallFlex (SEMS) and WallFlex-Soft (SEMS)	22 mm × 6 cm 22 mm × 9 cm 22 mm × 12 cm
Boston Scientific	AXIOS (LAMS)	10 mm × 10 mm 15 mm × 10 mm 20 mm × 10 mm
Cook Medical	Evolution (SEMS)	22 mm × 6 cm 22 mm × 9 cm 22 mm × 12 cm
Olympus America	Hanarostent (SEMS)	22 mm × 6 cm 22 mm × 9 cm 22 mm × 12 cm

[a] *LAMS* lumen-apposing metal stent, *SEMS* self-expanding metal stent

Enteral Stent Placement

Enteral stent placement refers to the endoscopic placement of a self-expanding metal stent (SEMS) across the point of luminal obstruction. SEMS is typically made of nickel-titanium (Nitinol) alloy and is designed to be constrained on a delivery catheter, then expand to their desired shape once the stent has been deployed. Although SEMS can be either covered or uncovered, current commercially available duodenal SEMS in the USA is universally uncovered (WallFlex [Boston Scientific, Marlborough, MA], Evolution [Cook Medical, Bloomington, IN], and Hanarostent [Olympus America, Center Valley, PA]) (Table 15.2).

Technique

Enteral stent placement is performed under fluoroscopic guidance and using a therapeutic gastroscope capable of handling the large diameter stent delivery catheters (Fig. 15.2). The area of stenosis is first examined endoscopically; typically, if a therapeutic endoscope is able to readily traverse across the stenosis, this implies that enteral stent placement should be avoided due to the risk of stent migration and subsequent bowel obstruction and/or perforation. Nevertheless, relative luminal narrowing, with or without focally compromised motility, can produce significant symptoms and the patient may still benefit from bypassing this area or from decompression. However, if the lumen is widely patent alternative diagnoses such as delayed gastric emptying should be considered.

While there are subtle variations in technique, we typically approach the stenosis using standard ERCP catheters such as sphincterotomes, cannulas, or balloon-extraction catheters, preloaded with a 0.035 inch semi-stiff guidewire. The guidewire is used to gently probe the stenosis under fluoroscopic guidance and identify the true lumen, taking care to avoid creating false tracts. The catheter is used to follow the guidewire, and contrast is injected to both confirm correct guidewire position and to delineate the length of the stenosis. After the stenosis has been properly measured, the catheter is exchanged over the guidewire for the stent delivery catheter containing an appropriately sized uncovered metal duodenal stent. The stent is then deployed under direct endoscopic and fluoroscopic guidance across the stenosis. After stent position is

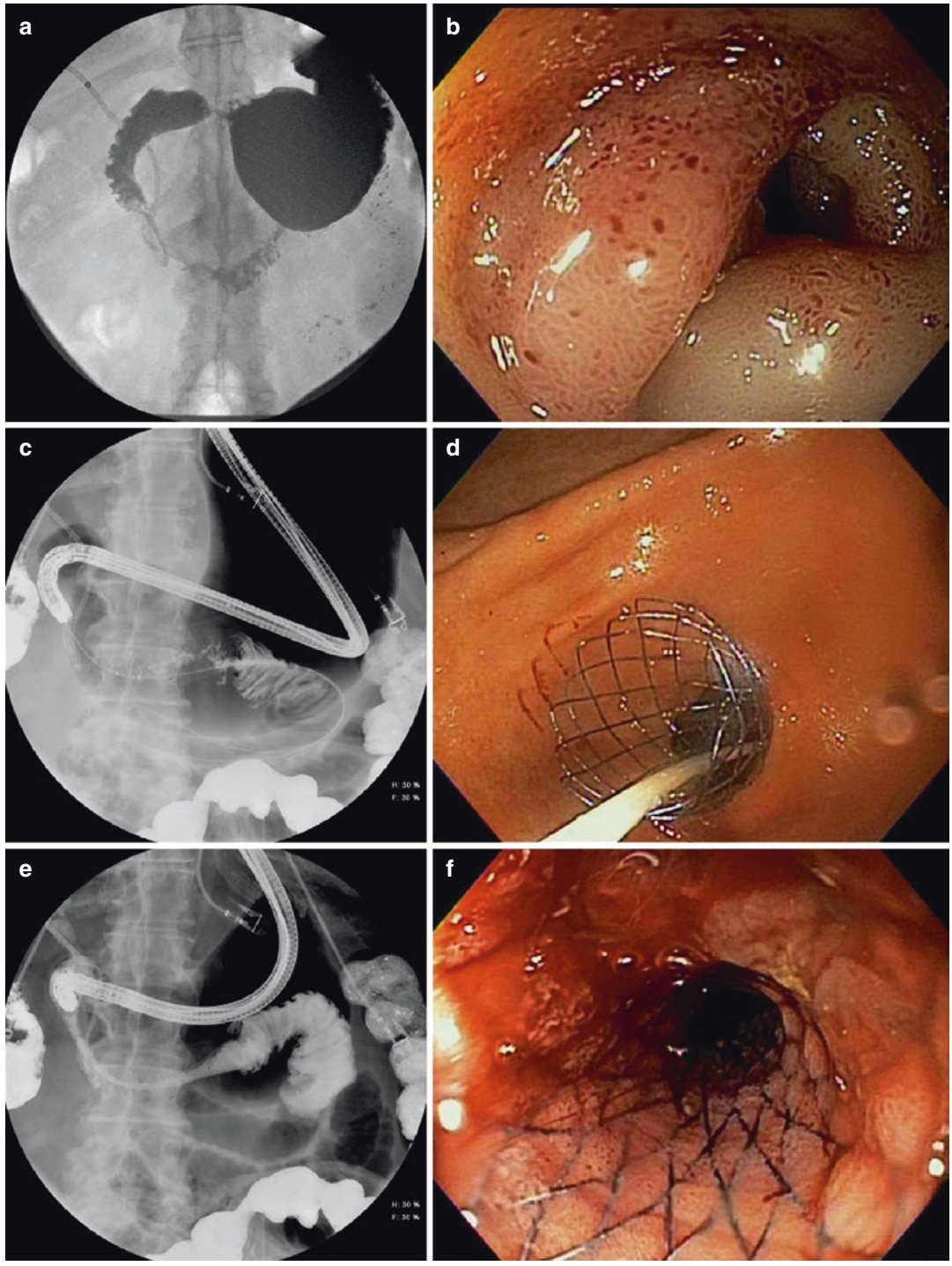

Fig. 15.2 Enteral stent placement. (**a**) Upper gastrointestinal series showing gastric outlet obstruction at the second portion of the duodenum due to pancreatic malignancy. (**b**) Endoscopic view of severe duodenal stricture in the second portion of the duodenum. (**c**) Fluoroscopic and (**d**) endoscopic views of stent deployment. (**e**) Fluoroscopic view of completed enteral stent deployment with contrast passage across the enteral stent into the distal duodenum. (**f**) Endoscopic view of completed enteral stent deployment

confirmed fluoroscopically, contrast can be injected across the stent to confirm luminal patency.

Outpatients who undergo enteral stenting can typically be discharged home following the procedure. Routine endoscopic follow-up is not typically necessary for patients who undergo enteral stent placement.

Outcomes and Efficacy

Endoscopic placement of a self-expanding metal stent was first described in 1992 [19]. The procedure rapidly became the standard procedure worldwide for patients with mGOO who are not otherwise candidates for surgical resection or surgical bypass, with multiple large systematic reviews, prospective studies, and randomized controlled trials to support its use [5, 7, 20–24].

Generally speaking, existing studies evaluating SEMS placement are limited by heterogeneous patient populations with various malignancies and treated with a large assortment of commercially available stents. A large systematic review of 32 studies demonstrated the technical success and clinical success of SEMS placement in patients with mGOO [20]. The mean survival time was 12 weeks (range, 1–184 weeks), technical success was 97% (range, 91–100%), and clinical success was 89% (range, 63–95%). Mean time to resumption of oral intake after SEMS placement was 4 days. Ultimately, 48% of patients were able to resume a full solid diet, 39% were able to tolerate soft solids, and 13% were unable to be advanced beyond full liquids. As such, we routinely warn patients undergoing enteral stent placement to expect limitations in oral intake, specifically avoiding high-fiber foods that may result in stent occlusion.

Despite their heterogeneity, studies evaluating SEMS placement in patients with mGOO uniformly show a large discrepancy between higher technical success rates and substantially lower clinical success rates which further decreases over time [22, 25–27]. The lower initial clinical success rate is believed to be attributed to a number of factors, which include gastrointestinal dysmotility (potentially from neural involvement by tumor), additional obstruction from peritoneal carcinomatosis, and generalized deconditioning and anorexia from underlying advanced malignancy. The continued decrease in clinical success rates over the long term is attributed to the inevitable development of stent-related complications such as tumor ingrowth and/or food impaction. Although enteral stent placement has been shown to improve obstructive symptoms, improvement in quality of life or performance status has not been consistently demonstrated [24, 28].

Adverse Events

Severe complications such as bleeding and perforation are rare and estimated to occur in approximately 1% of cases [5]. However, non-severe complications are common with enteral stent placement, estimated to occur in at least 25% of cases [5, 20]. These non-severe complications include stent malfunction, pain, and less commonly ampullary obstruction resulting in biliary obstruction, cholangitis, and/or pancreatitis.

Stent malfunction is the most common complication of enteral stent placement, occurring in at least 17% of cases and increasing with time [2, 5, 18]. Stents can malfunction due to tumor ingrowth, food impaction, or stent migration. Tumor ingrowth and recurrent mGOO are estimated to occur in the majority of patients who survive longer than 6 months after enteral stent placement and may require the insertion of additional stents (Fig. 15.3) [29]. Food impactions may require endoscopy for clearance. Stent migrations are uncommon in the USA where only uncovered duodenal SEMS are commercially available; however, worldwide, where both covered and uncovered SEMS are available, stent migration within 8 weeks of placement has been reported to be significantly more common with covered SEMS (up to 28%) [30]. Although migrated stents can be repositioned or removed when recognized early, completely migrated stents may cause downstream intestinal obstruction and/or perforation requiring emergency surgical intervention [31].

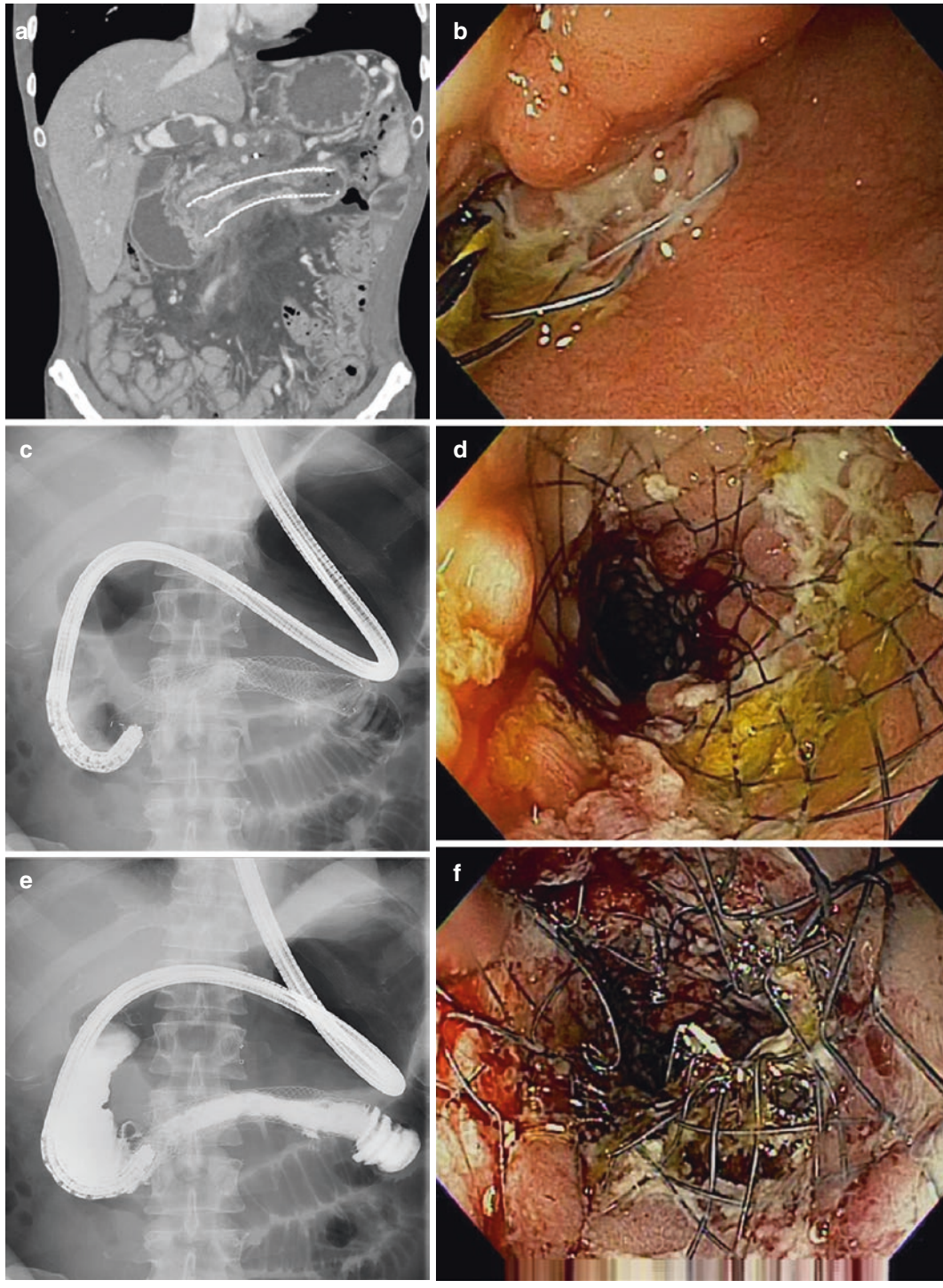

Fig. 15.3 Management of enteral stent malfunction due to tissue ingrowth. (**a**) Radiographic appearance of existing enteral stent with visible tissue ingrowth in a patient with pancreatic malignancy. (**b**) Endoscopic view of malfunctioned existing enteral stent with severe tissue ingrowth. (**c**) Fluoroscopic and (**d**) endoscopic views of stent deployment. (**e**) Fluoroscopic view of completed enteral stent deployment with contrast passage across the enteral stent into the distal duodenum. (**f**) Endoscopic view of overlapping enteral stents

Pain after enteral stent placement is most often due to expansion of the SEMS. As the SEMS takes approximately 48–72 h to fully expand, pain usually improves slowly over that interval. However, acute pancreatitis has uncommonly been reported to occur due to occlusion of the ampullary orifice by the duodenal SEMS [32].

Occlusion of the ampullary orifice by the duodenal SEMS may also result in biliary obstruction and/or cholangitis. Therefore, ERCP with biliary SEMS placement should be considered prior to duodenal SEMS placement in patients with mGOO who also have known or impending biliary obstruction [5]. Despite this, patients who have biliary SEMS who subsequently undergo duodenal stent placement have also been described to be at increased risk for biliary stent dysfunction; in a large series of patients with biliary stents, 52% of patients who underwent duodenal stent placement experienced biliary stent dysfunction [33].

Enteral Stents Versus Surgical Gastrojejunostomy

There has been considerable debate with regard to comparing enteral stents versus surgical gastrojejunostomy for the management of mGOO, with three randomized controlled trials [21–23], a large Cochrane review [7], and multiple additional systematic reviews and meta-analyses [18, 34]. Overall, they suggest that surgical gastrojejunostomy is superior to enteral stent placement and should be preferred in patients with acceptable life expectancy and good performance status.

Among the three randomized controlled trials, one showed improvement in quality of life with enteral stent but not with surgical bypass [23], whereas another did not show a difference between the two groups [22]. All three trials showed comparable rates of technical success and mortality, but longer hospital stay with surgery. Enteral stent placement was associated with more rapid improvement in symptoms [21, 22]. However, the largest randomized study with longest follow-up showed that late complications such as need for re-intervention were more common with enteral stent placement than surgical gastrojejunostomy, leading the authors to conclude that surgical gastrojejunostomy is preferable for patients with life expectancy of 2 months or longer [22]. These findings were subsequently confirmed in a Cochrane systematic review [7]. By pooling the data from the three randomized controlled trials, comprising 84 patients including 41 patients randomized to surgical palliation and 43 patients randomized to enteral stents, the authors concluded that enteral stent placement has the benefit of quicker resumption of oral intake and reduced inpatient hospital stay, however with higher recurrence rate and increased need for re-intervention.

Multiple meta-analyses have additionally compared surgical bypass with enteral stent placement. Recently, Mintziras et al. in 2019 reported a large systematic review and meta-analysis which included 27 studies and 2354 patients, of which 55.5% underwent enteral stent placement and 44.5% underwent surgical gastrojejunostomy [18]. The authors found that postoperative mortality and major complications were similar in the two groups. Surgical gastrojejunostomy was associated with significantly longer survival than enteral stent placement, with a mean difference of 43 days. Although the mean time to oral intake and length of hospital stay favored the enteral stent group, the frequency of re-interventions was nearly three times higher in the enteral stent group. It is worth noting, however, that existing studies have significant heterogeneity with regard to baseline patient clinical status, which may in turn influence reported clinical outcomes.

From a cost-effectiveness standpoint, studies have shown that enteral stenting is more cost-effective than surgical gastrojejunostomy [35, 36]. A decision-analysis study comparing surgical gastrojejunostomy and endoscopic stenting showed that over a 1-month period, enteral stent placement was the most cost-effective strategy with the lowest rate of complications and the highest success rate [37]. Therefore, although

surgical gastrojejunostomy is more durable, enteral stent placement is more appropriate for patients with either a short life expectancy or poor performance status.

EUS-Guided Gastroenterostomy

Recently, EUS-guided gastroenterostomy (EUS-GE) with placement of an electrocautery-enhanced lumen-apposing metal stent (LAMS) has emerged as a novel alternative procedure that may offer long lasting patency with fewer incidence of stent failure. Currently, the only commercially available LAMS in the USA is the AXIOS stent (Boston Scientific), although worldwide several additional options are available (Spaxus [Taewoong Medical, Gyeonggi-do, South Korea] and Nagi [Taewoong Medical]) (Table 15.2).

Technique

EUS-GE is typically performed under fluoroscopic guidance and using a linear-array therapeutic echoendoscope in order to handle the large diameter of the LAMS delivery catheter (Fig. 15.4). There are multiple different variations in EUS-GE technique, of which we will describe the most common approaches [38].

We have typically utilized a "freehand" or "direct" anterograde EUS-GE technique. In this approach, a standard ERCP cannula preloaded with a 0.035 inch semi-stiff guidewire is guided across the obstruction into the distal duodenum/proximal jejunum, followed by injection of approximately 600 mL of sterile water mixed with iodinated contrast and methylene blue. The patient is also administered 0.5–1 mg of glucagon to reduce intestinal peristalsis. In other variants of the technique a naso-jejunal tube is used to instill fluid throughout the procedure. The echoendoscope is then positioned along the greater curvature of the gastric body. From this location, the distended loop of small bowel can be identified both endosonographically and fluoroscopically. An electrocautery-enhanced LAMS is deployed in a "freehand" fashion into the jejunum under endosonographic and fluoroscopic guidance, thus establishing the gastroenterostomy. Following successful deployment, correct stent positioning is confirmed endoscopically and fluoroscopically. We then typically dilate the LAMS with a standard dilation balloon, and inject contrast across the LAMS both to confirm luminal patency and to rule out contrast extravasation which would imply intraprocedural perforation.

Occasionally, the linear echoendoscope may be able to traverse across the malignant obstruction. When that occurs, a direct "retrograde" EUS-GE approach can be considered. With this approach, the linear echoendoscope is in the distal duodenum, and the LAMS is deployed in retrograde fashion into the stomach (i.e. EUS-enterogastrostomy or EUS-EG). While this situation is uncommon, this approach is less technically demanding as the stomach is a larger and more stable target for electrocautery-enhanced LAMS puncture than the small bowel.

With the "freehand" technique, we do not routinely access the target jejunum first under EUS, nor do we first place a guidewire across the proposed gastroenterostomy tract. This avoids the dangerous situation in which the small bowel is paradoxically pushed away from the stomach by the guidewire, which increases the risk of subsequent LAMS misdeployment and perforation.

An alternative EUS-GE technique is known as the "balloon-assisted" technique. Using this technique, a dilating balloon is passed over a guidewire into the small bowel, which is then inflated with a mixture of contrast and saline while positioned in the duodenum and/or jejunum. The fluid-filled balloon is identified under EUS with the echoendoscope in the stomach. The balloon is then punctured under EUS guidance using a 19-gauge fine needle aspiration (FNA) needle. The bursting of the balloon indicates correct positioning of the needle tip within the small bowel lumen. At that point, a second guidewire is

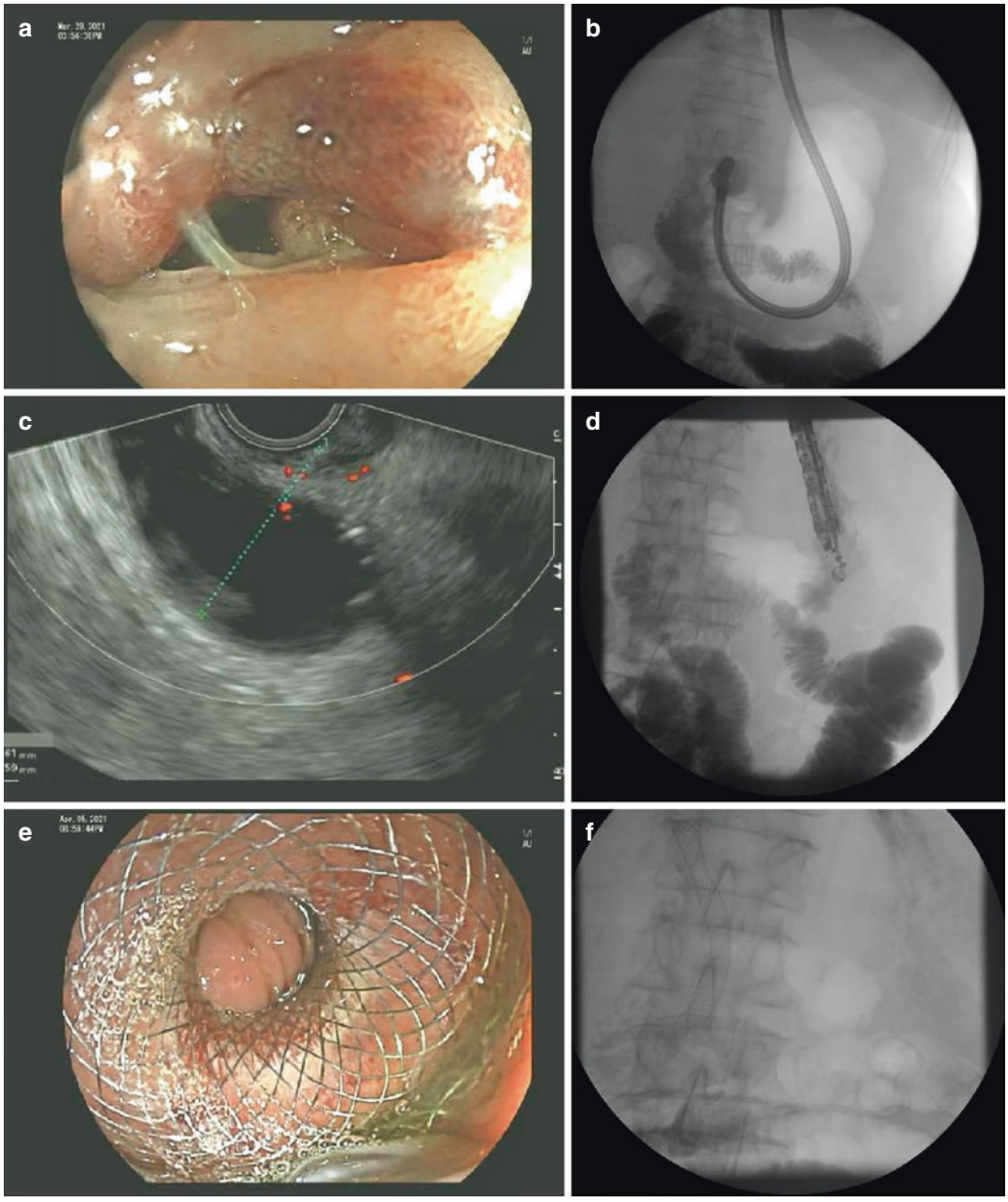

Fig. 15.4 EUS-guided gastroenterostomy (EUS-GE). (**a**) Endoscopic and (**b**) fluoroscopic views of guidewire passage across a severe duodenal stricture in the second portion of the duodenum. (**c**) Endosonographic and (**d**) fluoroscopic views of LAMS deployment. (**e**) Endoscopic and (**f**) fluoroscopic views of completed EUS-GE

advanced across the FNA needle and advanced into the jejunum, and a LAMS is subsequently deployed over the guidewire, thus creating the gastroenterostomy. In a different variation of this technique known as the rendezvous EUS-GE method, the puncturing guidewire can be trapped in the dilating balloon and then pulled back through the duodenal obstruction and out of the mouth, and a LAMS is subsequently deployed over the guidewire.

In Japan, a novel double balloon device (EUS-guided balloon-occluded gastrojejunostomy bypass; EPASS) was developed by Itoi et al. specifically to facilitate EUS-GE [39–41]. The device is not commercially available in the USA. The device consists of two balloons, connected by an enteric tube. Using this technique, a 0.089 inch guidewire is first passed as far into the small bowel as possible under standard endoscopy. The endoscope is exchanged over the guidewire, and subsequently the double balloon enteral tube is advanced over a guidewire into the small bowel. The two balloons are positioned in the duodenum and jejunum in an area adjacent to the stomach and then inflated using saline and contrast in order to anchor the small bowel. A mixture of saline and contrast is then injected into the intervening small bowel between the two balloons via the enteric tube, thus distending and stabilizing the segment of small bowel lumen. Subsequently, the echoendoscope is introduced and freehand EUS-GE is performed using an electrocautery-enhanced LAMS to create the gastroenterostomy.

EUS-GE can be combined with EUS-guided biliary drainage to allow for same session double endoscopic bypass for combined malignant gastric outlet obstruction and biliary obstruction [42, 43].

We routinely hospitalize all patients who undergo EUS-GE for observation following the procedure and prescribe a 7-day course of broad-spectrum antibiotics. For those EUS-GE patients who survive beyond 6 months, we consider repeat endoscopy to exchange the LAMS given concern regarding breakdown of the plastic coating within the metal stent, which can subsequently result in tissue ingrowth and eventual stent obstruction.

Outcomes and Efficacy

Since the early EUS-GE work using LAMS starting in 2012, multiple studies have evaluated the outcomes and efficacy of EUS-GE in the setting of mGOO, as well as comparing EUS-GE versus surgical gastrojejunostomy and versus enteral stent placement [39, 44, 45]. However, the literature has generally been sparse with regard to EUS-GE and the procedure has yet to achieve widespread adoption for multiple reasons including its technical difficulty, procedural risks, and lack of standardization.

The safety and efficacy of EUS-GE were reported in a recent systematic review and meta-analysis by McCarty et al. [46]. A total of 5 large studies comprising of 199 patients were included in the analysis, which included four retrospective studies and one prospective study [25, 47–50]. Among the patients included, 78% were patients with mGOO, and the majority (67%) were performed using a direct EUS-GE method, followed by 18% performed using a balloon-assisted method and 10% performed using the EPASS device. Immediate technical success was achieved in 92.9%, with clinical success achieved in 90.1%. Serious adverse events occurred in 5.6% of cases, related to perforation, peritonitis, bleeding, and abdominal pain. The overall adverse event rate was reported to be 10.6%. Over a mean follow-up period of 4.3 months, the re-intervention rate was 11.4%.

Only one study thus far has directly compared the efficacy of various EUS-GE techniques and was reported by Chen et al. [48] The study included a total of 74 patients from seven centers (six from the USA, one from Europe), of which 52 underwent direct EUS-GE, and 22 underwent balloon-assisted EUS-GE. The study showed similar technical success (94.2% vs 90.9%), clinical success (92.3% vs 90.9%), and adverse events (5.8% vs 9.1%) between the direct and balloon-assisted groups. Postprocedure length of stay, need for re-intervention, and survival were similar between the two groups. However, mean procedure time was significantly shorter with the direct EUS-GE technique compared to the balloon-assisted technique (35.7 vs 89.9 min), leading the authors to suggest that this may be the preferred method for EUS-GE.

EUS-GE Versus Surgical Gastrojejunostomy

Several studies have compared EUS-GE versus surgical gastrojejunostomy for the management

of mGOO [51, 52]. Overall, they suggest that EUS-GE is a non-inferior and less invasive alternative to surgical gastrojejunostomy.

Khashab et al. reported a multicenter retrospective study comparing 30 patients who underwent EUS-GE versus 63 patients who underwent surgical gastrojejunostomy [51]. Technical success was significantly higher in the surgical gastrojejunostomy group compared with EUS-GE (100% vs 87%). However, there was no statistically significant difference in clinical success (90% vs 87%), adverse events (25% vs 16%), length of hospital stay (12 vs 11.6 days), rate of recurrence (14% vs 3%), or time to re-intervention (121 vs 88 days) between the surgical gastrojejunostomy and EUS-GE groups.

Similarly, Perez-Miranda et al. reported a multicenter retrospective study comparing 25 patients who underwent EUS-GE versus 29 patients who underwent laparoscopic gastrojejunostomy [52]. There was no statistically significant difference in technical success (100% vs 88%) or clinical success (90% vs 84%) between the surgical gastrojejunostomy and EUS-GE groups. However, surgical gastrojejunostomy was associated with increased procedure time (178 vs 77 min), higher adverse events (41% vs 12%), and higher estimated costs ($14,778.80 vs $4515.00) compared to EUS-GE.

EUS-GE Versus Enteral Stents

Several studies have compared EUS-GE versus enteral stenting for the management of mGOO [25, 53]. Overall, they suggest that EUS-GE may be offered for select patients with mGOO in centers with extensive experience in the procedure.

Chen et al. reported a multicenter retrospective study comparing 30 patients who underwent EUS-GE from 2013 to 2015 versus 52 patients who underwent enteral stent placement from 2008 to 2010. The study showed no statistically significant difference in technical success (86.7% vs 94.2%), clinical success (83.3% vs 67.3%), and adverse events (16.7% vs 11.5%) between the EUS-GE and enteral stent groups. However, symptom recurrence and need for re-intervention were significantly lower in the EUS-GE group compared to the enteral stent group (4.0% vs 28.6%), and on multivariable analysis, enteral stent placement was independently associated with need for re-intervention.

Recently, our group reported a more contemporary experience comparing the clinical outcomes and adverse events between EUS-GE and enteral stent placement in patients with mGOO [25]. In an effort to minimize heterogeneity among existing stents and techniques, we compared 22 patients who underwent EUS-GE specifically using the electrocautery-enhanced AXIOS LAMS, versus 78 patients who underwent enteral stent placement specifically using current generation enteral stents (Boston Scientific WallFlex or Cook Evolution). Among these patients, 50.0% had ascites, and 50.0% had evidence of peritoneal carcinomatosis on cross-sectional abdominal imaging. Technical success was achieved in 100% in both EUS-GE and enteral stent groups. However, initial clinical success was higher among patients undergoing EUS-GE compared to enteral stent placement (95.8% vs 76.3%, $p = 0.042$), with a trend towards lower number of adverse events (20.8% vs 40.2%, $p = 0.098$). Additionally, a lower rate of stent failure requiring repeat intervention was observed among patients undergoing EUS-GE compared to enteral stent placement (8.3% vs 32.0%, $p = 0.021$). Kaplan–Meier survival curve analysis furthermore demonstrated greater stent durability among patients who underwent EUS-GE ($p = 0.013$). The length of hospital stay was similar between the two procedures, with no reported incidences of postprocedure ileus.

As previously mentioned, a "double bypass" can be performed endoscopically, using a combination of EUS-GE and EUS-guided choledochoduodenostomy, to allow for same session endoscopic management of combined mGOO and malignant biliary obstruction. This was first demonstrated by our group and subsequently in a small case series [42, 43].

Adverse Events

LAMS misdeployment resulting in perforation is currently the most feared adverse event in EUS-GE and is the single adverse event that has most hindered the standardization of the technique and limited both its adoption and dissemination. Failed electrocautery-enhanced LAMS puncture and subsequent LAMS misdeployment can result in perforation of both the gastric and jejunal lumens. Even a minor slippage of the LAMS can result in pneumoperitoneum and peritonitis. While gastric perforation can typically be endoscopically closed without difficulty, the jejunal perforation is often not endoscopically accessible. As such, salvage of a failed EUS-GE can be an arduous task, sometimes requiring NOTES (natural orifice transluminal endoscopic surgery) rescue with direct endoscopic examination of the peritoneal cavity [54, 55]. An unsuccessful salvage results in either emergency surgery or can be fatal. Therefore, fear of LAMS misdeployment and perforation has limited EUS-GE to only select tertiary care centers, with limited training opportunities and an undefined learning curve.

The rate of LAMS misdeployment and/or perforation varies from the available studies, ranging from 6.8% reported by Chen et al. to up to 36% reported by Perez-Miranda et al. [52, 53] In our study, misdeployment resulting in perforation occurred in 8.3% of EUS-GE cases [25]. In the reported literature, most cases of misdeployment were salvaged endoscopically; however, occasionally surgical intervention was necessary.

Other adverse events related to EUS-GE include hemoperitoneum, LAMS migration, and LAMS tissue ingrowth. Hemoperitoneum is likely due to inadvertent puncture of extraluminal vessels during LAMS deployment and can be severe, requiring urgent angiography and embolization. LAMS migration has been uncommonly described. Finally, LAMS tissue ingrowth has been described among patients who survived greater than 6–9 months after initial LAMS placement. This is due to the eventual breakdown of the plastic covering within the LAMS, which results in the stent becoming uncovered. In our study, LAMS mesh erosion occurred in 4.2% of EUS-GE cases and was managed with stent replacement [25].

Venting Gastrostomy

Placement of a venting gastrostomy tube is indicated where all available surgical and endoscopic options have been exhausted. This technique is usually reserved as a "last resort," given that venting gastrostomy tube placement does not provide nutrition to the patient. Nutritional supplementation will be necessary with either separate jejunostomy placement, or initiation of total parenteral nutrition (TPN), the latter of which is controversial due to risks of infection and ethical questions regarding futility.

Various endoscopic and radiographic techniques of gastrostomy tube placement have been described [56]. In the traditional "pull" technique, an upper endoscopy is first performed, and a suitable location is identified via transillumination or manual palpation in the left upper abdomen. A finder needle is placed into the stomach under endoscopic visualization, and a guidewire is passed percutaneously into the stomach. The guidewire is endoscopically grasped and pulled out through the patient's mouth. A skin incision is made at the guidewire entry site. The guidewire is then attached to a gastrostomy tube at the oral side, and the guidewire is pulled from the abdomen side, such that the tube traverses down the patient's mouth, esophagus, and proximal stomach before exiting via the abdominal skin incision. Typically, a large caliber gastrostomy tube (i.e. 24-French) is preferred for venting purposes to reduce the risk of the tube being clogged with solid gastric contents.

Following tube placement, patients experience immediate improvement in symptoms due to complete decompression of the stomach. However, patients typically are instructed to take predominantly a liquid diet, for fear of clogging the gastrostomy tube. Recently, a large caliber

aspiration tube (V-Tube, Aspire Bariatrics, King of Prussia, PA) has been approved for use in gastric decompression [57]. Originally developed for endoscopic bariatric therapy, the tube is 28-French in diameter, with a fenestrated intragastric portion that sits in the gastric fundus. The purpose of the device is to allow patients access to a regular diet with decreased risk of clogging.

The clinical efficacy of decompressive gastrostomy is well-documented, with approximately 90% rate of symptom relief and avoidance of nasogastric decompression [58, 59]. Adverse events related to gastrostomy include skin-site issues such as skin infection, overgrowth of granulation tissue, and leakage of gastric contents, and tube-related issues such as clogging, accidental dislodgement, and the "buried bumper syndrome." In a study comparing radiographic versus endoscopic gastrostomy, radiographic gastrostomy was noted to have higher 30-day complication rates than endoscopic gastrostomy (23% vs 11%), which included infection and inadvertent tube removal [60]. Ascites is traditionally considered a relative contraindication to gastrostomy tube placement; however, paracentesis prior to the procedure may facilitate successful placement with low adverse event rates [61].

Special Considerations

mGOO in the Post-Whipple Anatomy

The management of mGOO is more challenging in the post-Whipple patient due to the postsurgical anatomy, and options are limited in this setting, especially as mGOO often occurs in conjunction with delayed gastric emptying [62]. When mGOO arises at the level of the gastrojejunostomy, endoscopic options include either enteral stent placement (into alimentary +/− pancreaticobiliary limbs), or venting gastrostomy tube placement.

Delayed Gastric Emptying

Approximately 60% of patients with pancreatic cancer have evidence of delayed gastric emptying, without evidence of direct tumor invasion [63]. This is believed to be due to tumor infiltration into the nerve plexuses. The presenting symptoms may mimic those of mGOO, leading to progressive anorexia, nausea, and vomiting. The diagnosis can be made either on a gastric emptying study or as a diagnosis of exclusion when endoscopically ruling out mechanical obstruction. In these cases, enteral stent placement or gastrojejunostomy is ineffective in relieving symptoms and should be avoided.

Delayed gastric emptying in the setting of pancreatic cancer is often challenging to manage. Prokinetic agents such as metoclopramide may be beneficial [63]. However, patients with delayed gastric emptying will often require decompressive (venting) gastrostomy tube placement. A combined gastrostomy/jejunostomy tube can palliate both symptoms of delayed gastric emptying, as well as provide postpyloric enteral nutrition. However, combined tubes may fail due to reflux of the jejunostomy attachment back into the stomach, requiring endoscopic revision. As such, in our practice, a venting gastrostomy tube placement is often combined either with a separate jejunostomy tube placement (placed either percutaneously via interventional radiology, or surgically) or with initiation of total parenteral nutrition (TPN) in patients who cannot undergo jejunostomy tube placement.

Summary and Management Algorithm

Malignant GOO is both a distressing condition for the patient and a therapeutic challenge for the gastroenterologist and oncologist. Until recently, mGOO was treated either with surgical gastroenterostomy or enteral stent placement. Advancements in therapeutic EUS have allowed for the development of novel procedures such as EUS-GE, an endoscopic analogue to surgical gastroenterostomy, allowing for complete enteral bypass around the region of the malignancy without the substantial morbidity and mortality associated with surgical intervention in complex and often severely ill oncological patients. Table 15.3 summarizes the currently available treatment modalities.

Table 15.3 Comparison of treatment modalities in the management of malignant gastric outlet obstruction

Modality	Benefits	Risks
Surgical gastrojejunostomy	• Standard palliative surgical option • Longest durability, best option for patients with good performance status and reasonable life expectancy • May be combined with operative biliary bypass	• Most invasive • Delayed gastric emptying and postoperative ileus may occur in up to 58% of patients • Additional more serious risks include anastomotic leakage • Longest procedure-related hospital stay
Enteral stent placement (SEMS)	• Standard palliative endoscopic option • Least technically demanding, excellent technical success, and high initial clinical success • Stent malfunction can be managed with insertion of additional stents • Best option for patients with limited life expectancy or poor performance status	• Initial clinical success decreases over time, with stent malfunction and tissue in growth occurring in majority of patients beyond 6 months • Additional risks include pain, biliary obstruction, cholangitis, pancreatitis, stent migration, and perforation
EUS-guided gastroenterostomy (LAMS)	• Novel palliative endoscopic option • Endoscopic analogue to surgical gastrojejunostomy • May be considered as alternative to enteral stents in patients with reasonable life expectancy but poor surgical candidate • May be combined with EUS-guided biliary drainage	• Highly technically challenging, limited to centers of expertise • Yet to achieve widespread adoption due to procedural risks, technical difficulty, and lack of standardization • Most dreaded risk is stent misdeployment/perforation which may require surgical rescue • Additional risks include hemoperitoneum, stent migration, and tissue ingrowth
Venting gastrostomy	• Highly effective for gastric decompression	• Option of last resort, as venting gastrostomy does not allow nutrition • Risks include tube-related issues such as clogging and dislodgement, and skin-site issues such as infection and leakage

We typically advocate for the following management algorithm (Fig. 15.5). When mGOO is suspected based on either clinical history and/or cross-sectional abdominal imaging, nasogastric decompression is first performed to completely empty the stomach. During this time, consultation should be obtained with both the patient's primary medical and surgical oncologist. A frank discussion with the patient should involve the risks and benefits of surgical gastrojejunostomy, enteral stent placement, and novel strategies such as EUS-GE.

Typically, in a patient with otherwise good performance status and reasonable life expectancy, bypass with either surgical gastrojejunostomy or EUS-GE should be considered due to superior long-term durability as compared with enteral stent placement. Given its inherent risks, complex procedures such as EUS-GE should only be offered at select centers with expertise in the technique. Even in expert hands, EUS-GE has potentially serious risks of small bowel perforation and stent misdeployment, both of which can pose significant challenges to the endoscopist and which may require surgical rescue. Enteral stent placement should be reserved for cases where surgical gastrojejunostomy or EUS-GE is not possible.

When a patient is not a candidate for surgical gastrojejunostomy due to poor performance status or has limited life expectancy, either EUS-GE or enteral stenting can be considered. EUS-GE is preferred to enteral stenting, in centers with this expertise, due to better symptom control and less need for re-intervention. We recommend enteral stent placement in patients where an acceptable window cannot be identified for EUS-GE due to distance between bowel walls, intervening vascu-

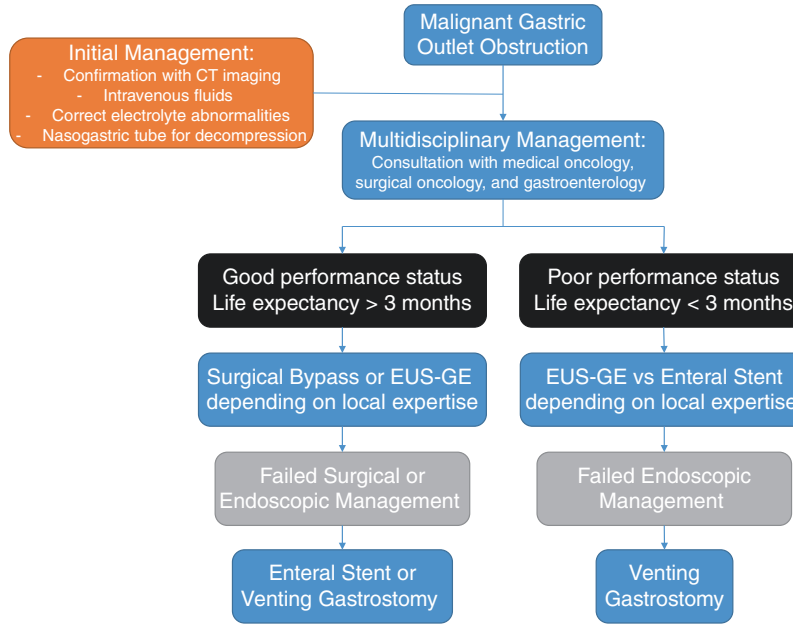

Fig. 15.5 Proposed management algorithm

lature, ascites, or other technical reasons. Venting gastrostomy is reserved only as a last resort when the patient has exhausted all surgical and endoscopic options.

Ultimately, the management of mGOO is multidisciplinary in nature. By approaching the condition in a collaborative fashion, an optimal treatment plan can be crafted and personalized based on the patient's immediate clinical situation and overall picture.

Disclosures

Phillip S. Ge: Nothing to disclose.

Christopher C. Thompson: Boston Scientific (Consultant), Medtronic (Consultant), USGI Medical (Consultant, Advisory Board Member, Research Support), Olympus (Consultant, Research Support), Apollo Endosurgery (Consultant, Research Support), GI Windows (Ownership Interest), Aspire Bariatrics (Research Support), Fractyl (Consultant, Advisory Board Member), Spatz (Research Support), EndoTAGSS (Ownership Interest), GI Dynamics (Consultant).

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16 Pain Control: Celiac Plexus Neurolysis

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Pancreatic cancer has one of the worst prognosis of all solid carcinomas. The estimated 5-year survival rate for pancreatic cancer is less than 5%; and more than half of patients do not survive beyond 1 year [1–3]. Over 80% of patients with pancreas cancer experience substantial abdominal pain, which frequently becomes difficult to control in those with unresectable disease [4–6]. Furthermore, pain severity also correlates with decreased survival. Pain control is one of the major goals of palliative care in patients with advanced pancreatic cancer.

Conventionally, pain is alleviated using nonsteroidal anti-inflammatory agents and/or opioid analgesics, following the three-step analgesic ladder pain management strategy recommended by the World Health Organization [7]. However, pain is difficult to control in some cases, presenting a challenge to the physician. Furthermore, some patients experience serious drug-related side effects that can markedly reduce their quality of life. Under such circumstances, celiac plexus neurolysis (CPN), in which the celiac plexus (CP) is chemically ablated, has been widely performed as an alternative treatment for alleviating cancer-associated pain [8].

The celiac plexus, composed of the celiac ganglia and a network of nerve fibers, is the largest splanchnic plexus in the human body. Afferent fibers that transmit pain from the intra-abdominal viscera directly enter the celiac plexus and then travel up the splanchnic nerves to the dorsal root ganglia, whence they continue to travel up the spinal cord to the cerebral cortex. We can relieve the pain by ablating or blocking the neural pathway. CPN is the permanent ablation of the celiac plexus with phenol or alcohol, and it is usually used in patients with malignant disease. CPN involves injecting a neurolytic agent (e.g., absolute alcohol, phenol) around and/or into the celiac plexus neural network of ganglia to prevent propagation of pain signals from the pancreas and nearby visceral organs. The goal of CPN is to lower abdominal pain levels, mitigate narcotic requirements, and thereby improve the quality of life.

Celiac plexus block (CPB) is the temporary inhibition of the celiac plexus. CPN and CPB techniques are identical. The only differences are with respect to clinical indications and the materials injected. The former classically involves destruction of the celiac plexus by injection of a neurolytic agent (with or without an anesthetic agent such as bupivacaine). The latter involves

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_16

the injection of an anesthetic, with or without steroids, and no neurolytic agent. CPN has been used in patients with pancreatic cancer and chronic pancreatitis, while CPB has only been used in patients with chronic pancreatitis [9–14].

Some studies have suggested that visualization of the ganglia is possible in approximately 80% of patients [15–18], and when this occurs, direct injection of alcohol into the ganglia rather than random injection into the space between the aorta and the celiac trunk can be performed [19]. Some studies comparing celiac ganglia neurolysis (CGN) with CPN suggest that patients in the CGN group experienced greater pain relief within 3 months after injection, a lower treatment failure rate, and faster onset and longer duration of pain relief than those in the CPN group [20–22].

Current imaging modalities can be used to guide CPN, such as X-ray imaging, computed tomography (CT), MRI, transabdominal ultrasound, and endoscopic ultrasound (EUS).

Percutaneous Celiac Plexus Neurolysis

The advantages and disadvantages of the various imaging modalities are shown in Table 16.1.

Among these, CT guidance is the preferred modality, as it can clearly display the celiac plexus and its surrounding blood vessels, organ structure, and puncture needle. Compared to the other percutaneous modalities, the endoscopic ultrasound (EUS) method is a more recently developed but well-established technique, which may have unique benefits. Hence, percutaneous CPB/CPN is briefly discussed [23–38].

Method

Percutaneous CPN may be performed from either a posterior or an anterior approach based on the patient's position and the site of needle introduction.

Anterior Approach

Although initially reported as early as 1918, the anterior approach generally remains a second-line approach given the higher risk of visceral organ injury. Advantages to the anterior approach include overall ease and speed and a lower probability of neurologic injury. Risks are largely secondary to visceral organ damage and include infection, hemorrhage, fistula formation, liver hematoma, and gastric perforation. Of note, the

Table 16.1 Imaging modalities used to guide celiac plexus neurolysis (CPN)

Modality	Advantages	Disadvantages
Non-imaging-guided	No need for imaging-compatible equipment	High incidence of complications
Intraoperative injection	Neurolytic solutions are injected directly into the celiac ganglia.	Performed during pancreatic resection surgery
X-ray-guided	Shows the spatial relationship between the vertebral body and puncture needle	Low resolution/risk of paraplegia/cannot clearly show the plexuses, pancreas, blood vessels, tumors, nerve damage
CT-guided	Clearly displays the celiac plexus and its surrounding blood vessels, organ structure, and puncture needle	Ionizing radiation/images are affected by scattering artifact of the metal puncture needle
MRI-guided	Distribution and course of celiac plexus are displayed clearly/free of ionizing radiation	Expensive/easy to be affected by motion artifact and metal
Ultrasound-guided	Observe the abdominal organs and blood vessels dynamically, real-time needle guidance	Low resolution/images are affected by gastrointestinal gas and somatotype
EUS-guided	High safety/minimal trauma/real-time dynamic/shortest puncture distance/incidence of complications is lower than percutaneous puncture approach	Not applicable to patients who cannot tolerate gastroscopy

anterior approach may also be performed under transabdominal ultrasound guidance.

Posterior Approach

Posterior approaches are more commonly performed, and multiple routes have been reported: the transcrural paravertebral, trans-intervertebral disc, and transaortic routes. The selection of various routes should be individualized based on operator's preference, patient's anatomy, and extent of disease.

The posterior transcrural paravertebral route is purportedly the most commonly utilized approach. The goal is direct ablation of the celiac plexus via injection of a neurolytic agent into the antecrural space. The ideal needle tip position is immediately anterolateral to the aorta at the level of the space between the celiac trunk and the superior mesenteric artery, anterior to the diaphragmatic crus, and posterior to the pancreas. The posterior trans-intervertebral disc approach is an alternative technique that can be used when the paravertebral route is obstructed, usually by the transverse processes, ribs, or abnormal retroperitoneal anatomy. This technique is precluded in patients with extensive degenerative disease of the thoracolumbar spine and is not considered first-line treatment given its associated risks of disc trauma (i.e., discitis or herniation). The posterior trans-aortic route has a low complication rate despite traversing two walls of the abdominal aorta. A theoretical advantage of the transaortic approach is minimization of the risk of neurologic complications resulting from the spread of the neurolytic agent to the lumbar plexus or spinal cord. The primary disadvantage is the increased risk of retroperitoneal hemorrhage accompanying iatrogenic aortic puncture, which may occur in up to 0.5% of patients, particularly those with hypertension or coagulopathy.

Complications

Table 16.2 reviews the possible adverse effects and complications of percutaneous CPN.

Table 16.2 Adverse effects and complications of percutaneous celiac plexus neurolysis

Technical	Physiological
Damage to somatic nerves • Paresthesia or deficit of lumbar somatic nerves Penetration of intervertebral foramen • Epidural injection • Paraplegia Trauma to great vessels • Intravascular injection • Vascular wall trauma • Vascular embolism or thrombosis Necrosis of tissue • Aorto-duodenal fistula Needle injury • Intradiscal injection • Renal injury • Pneumothorax • Chylothorax • Injection of psoas muscle • Retroperitoneal hematoma	Orthostatic hypotension—Celiac plexus ablation by neurolysis Diarrhea (unopposed parasympathetic activity) Urinary abnormality Impotence Paralysis Others • Local pain • Failure to relieve pain • Shoulder pain • Back pain • Ethanol intoxication Seizures • Loss of consciousness Infection • Abscess • Peritonitis

Risks include hypotension, diarrhea, vascular injection, spinal cord and nerve damage, retroperitoneal and visceral hematoma, abscess, and discitis. The two most common adverse effects are diarrhea and orthostatic hypotension due to the sympathectomy that occurs after a successful block. There have also been case reports of anterior spinal cord infarction causing paraplegia, as well as a fatality following EUS-guided CPN.

Endoscopic Ultrasound-Guided Celiac Plexus Neurolysis

In 1996, the first case series of endoscopic ultrasound (EUS)-guided CPN was reported [39]. Since the time it was described, EUS-CPN has been widely applied as a minimally invasive approach in treating pancreatic cancer-associated

pain. EUS-CPN is considered to be a safer approach than posterior percutaneous techniques because posterior spread of the neurolytic agent is minimized by the anterior method, and thereby, the risk of complications (e.g., paraplegia) may be reduced, and the effectiveness of the procedure may be potentially increased [40–44]. Additionally, staging and fine-needle aspiration of the pancreatic tumor can be performed at the same time. In a practice guideline for EUS-CPN, EUS-CPN was considered to control pain at least as well as percutaneous CPN [14].

Method

Instruments

1. Both linear and forward-view echo-endoscopes may be used for EUS-guided CPN.
2. Color and power Doppler techniques allow easy identification of vascular structures (in order to avoid inadvertent intravascular injection).
3. Standard aspiration needles (19 gauge [G], 22 G, 25 G) as well as a special 20-G injection needle may be used (Wilson-Cook, Winston-Salem, NC).

Drugs

1. Local anesthetics: 10 ml of 0.25% bupivacaine is commonly recommended. Local anesthetics can relieve pain quickly, but the duration of pain relief is brief. A single injection of local anesthetics (celiac plexus block) is used as an initial treatment by some. If the patients obtain short-term pain relief after the bupivacaine injection, one can then perform neurolysis later with alcohol or phenol. Others inject a neurolytic directly, and in that situation, injecting local anesthetics such as bupivacaine at first during the same procedure can reduce the transient pain resulting from EUS-guided neurolysis.
2. Absolute alcohol: 10–20 ml of 95–98% ethanol/99% alcohol is a common neurolytic agent for CPN. Because the celiac plexus damage is irreversible, the pain relief is long term. This technique is not sterile because the needle will cross the gastric wall into the celiac space, so the use of absolute alcohol can reduce the risk of infection.

Recently, Ishiwatari et al. [45] investigated the effectiveness of using phenol instead of alcohol for this procedure. The authors concluded that the use of highly viscous phenol-glycerol could provide excellent pain relief by enabling appropriate distribution of the neurolytic agent.

Procedure

Before the endoscopic procedures, pain scores are evaluated objectively using a visual analog scale, a numeric rating scale, or a 10-point Likert pain score.

Patients are placed in the left lateral position under moderate sedation induced by various combinations of intravenous midazolam, propofol, and/or fentanyl. The procedure is preceded by a preliminary intravenous infusion of 500–1000 cc of saline solution to prevent orthostatic hypotension. Antibiotic prophylaxis is also recommended. Patients who have severe coagulopathy should be excluded. For the entire procedure, blood pressure, oxygen saturation, and heart rate are continuously monitored.

Bilateral Approach (Fig. 16.1)

The linear-array echo-endoscope is introduced orally to visualize the origin of the celiac trunk. Then, the shaft is rotated clockwise or counterclockwise. The place where the root of the celiac trunk just disappears from view, but with the aorta still seen, is a reliable location of the celiac ganglia.

A syringe filled with 5 ml of sterile saline is attached to the hub of a 22-gauge needle that has been primed with saline. The needle is inserted into the channel of the echo-endoscope. Under EUS guidance, the needle tip is placed immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk. An aspiration test should be performed first to exclude the possibility that the needle has been acciden-

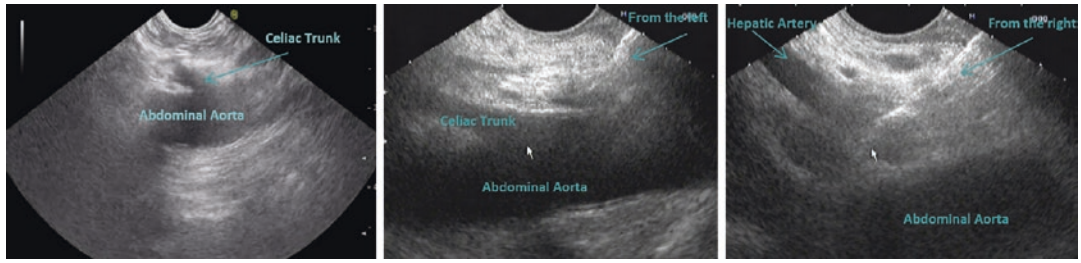

Fig. 16.1 Bilateral approach. The linear-array echo-endoscope is introduced orally to visualize the origin of the celiac trunk. Then, the shaft is rotated clockwise or counterclockwise. The place where the root of the celiac trunk just disappears from view, but with the aorta still seen, is a reliable location of the celiac ganglia. The injection is performed at this place. The above process is then repeated on the opposite side of the aorta

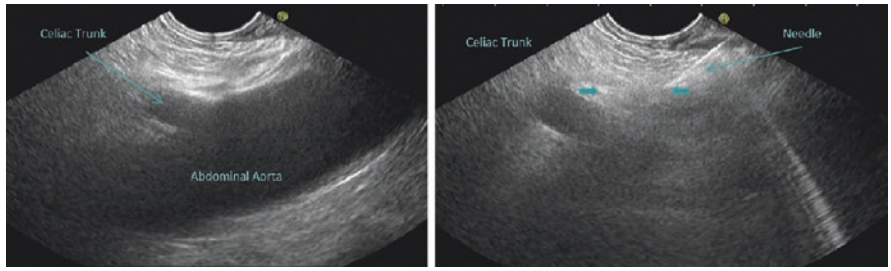

Fig. 16.2 Central injection approach. When performing the single-puncture approach, the tip is placed as close to the celiac trunk as possible. Hyperechoic structures can be seen after injection

tally inserted into a vessel. Because the needle lumen is narrow, the aspiration should last for 5–10 s.

If no blood is obtained from a short aspiration test, 10 ml of 0.25% bupivacaine is injected followed by 10–20 ml of 95–98% ethanol for neurolysis. Finally, the needle is flushed with 3 mL of saline and removed under visualization by EUS. The appearance of a dense cloud is typically identified by EUS after injection. Several minutes later, the patient's blood pressure may fall by 10–30 mmHg.

The above process is then repeated on the opposite side of the aorta.

Central Injection Approach (Fig. 16.2)

Some endosonographers prefer to perform single-puncture approach. The needle tip is advanced just superior to the takeoff of the celiac trunk, and the entire neurolytic agent is injected into the cephalad area of the celiac trunk. The neurolytic agent can spread around the celiac trunk. Compared with the dual-puncture approach, the effect of the single-puncture approach is similar, but the procedure time can be shortened.

Most commonly, the celiac trunk deviates to the right where it arises from the aorta. The left side is easier to puncture than the right side. The two-puncture approach is especially difficult to perform when the pancreatic tumor is large and presses on the celiac trunk. In this case, the single-puncture approach is preferred.

When performing the single-puncture approach, the tip is placed as close to the celiac trunk as possible. Therefore, an aspiration test should be performed carefully beforehand. If any blood is withdrawn, the procedure should be terminated, as injury of the celiac trunk may lead to splenic infarction. The CPN needle, which has side holes, may be helpful for avoiding injection into the vessel.

Results from a retrospective single-center study ($n = 160$) favored bilateral injections over a single central injection as the only predictor of >50% 7-day pain reduction [46]. Sub-group analysis in the meta-analysis of Puli et al. showed

pain relief in 84% of patients receiving bilateral injections vs. 46% of patients receiving central injections [47]. A study of 50 patients with pancreatic cancer randomized to receive single or bilateral injections of alcohol did not identify any difference in the onset or duration of pain relief [48]. Similar findings were reported in a retrospective study with no difference between central and bilateral techniques in the median pain reduction from baseline to 4 weeks post-procedure [49]. The assumption is that there is no difference between central vs. bilateral injections in EUS-guided CPN. In our opinion, if the local anatomic relationship is clear, we recommend the bilateral approach as the better choice. The single-puncture approach is preferred only when it is difficult to perform the two-puncture approach.

Complications

Adverse events related to EUS-guided CPN occur in up to 30% of cases, most commonly diarrhea (7%), an increase in abdominal pain (2–4%), and hypotension (4%). Symptoms are usually mild (grade I-II) and self-limiting [8, 50, 51].

Serious adverse events related to EUS-guided CPN (0.2%) and CPB (0.6%) have been reported and include bleeding, retroperitoneal abscess (in EUS-guided CPB), abdominal ischemia, permanent paralysis, and death (2 cases) [51]. The risk of serious morbidity and mortality should be weighed against expected benefits.

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Part V

Emerging Paradigms in Pancreatic Cancer

17 Minimally Invasive Surgical Approaches

Naruhiko Ikoma, Yuki Fujii, and Matthew H. G. Katz

Introduction

Minimally invasive surgery techniques have remarkably evolved over the past few decades in the field of surgical oncology, including for pancreatic malignancies [1–8]. Although experience is still in its nascence, the robotic surgery platform has overcome many limitations of the laparoscopic approach and accelerated widespread implementation of minimally invasive pancreatectomy. Advantages of the robotic platform include three-dimensional optics, maximized range of motion by endo-wrist articulation, augmented precision of technical skills, a stable camera platform, and surgeon ability to control four instruments. Minimally invasive pancreatectomy has been consistently associated with a shorter hospital stay, less blood loss, and equivalent complication rates compared with the open approach, if performed by expert surgeons at select high-volume institutions, on well selected patients. Improved short-term outcomes can accelerate the return to intended oncologic treatment [9] and may result in improved oncologic outcomes of pancreatic malignancies.

However, whether minimally invasive approaches can maintain the quality of certain aspects of oncologic surgical procedures, such as dissection around the superior mesenteric artery (SMA) and lymph node dissection around the common hepatic artery, as well as the generalizability of minimally invasive oncologic surgery outside of a few expert surgeons, remains unknown. Two recent prospective randomized controlled trials (RCTs) failed to prove non-inferiority of minimally invasive approaches in terms of surgical quality and survival outcomes after proctectomy for rectal cancer [10, 11], and one RCT showed inferior survival for the minimally invasive approach compared with the open approach in patients undergoing hysterectomy for cervical cancer [12]. The US Food and Drug Administration has publicly urged caution in the use of the robotic approach for cancer-related surgery [13]. Oncologic outcomes of minimally invasive pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) remain a matter of concern, and continued critical evaluation at the institutional, national, and international levels using prospective registries is warranted [14].

In this chapter, we review available evidence related to minimally invasive pancreatectomy with a focus on the two most common pancreatectomy procedures, distal pancreatectomy (DP) and pancreatoduodenectomy (PD), and we describe our effort at MD Anderson to successfully implement a minimally invasive foregut surgery program.

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_17

Minimally Invasive DP

Because of the relative simplicity of DP, which does not require reconstruction after resection, minimally invasive DP has been widely accepted and increasingly performed. Minimally invasive DP is reported to be safe and feasible for pancreatic malignancies, including PDAC [14, 15]. Large retrospective analyses as well as recent systematic reviews have shown that minimally invasive DP resulted in less blood loss and shorter hospital stays compared with open DP, and there were no significant differences in incidence rates of short-term complications, including postoperative pancreatic fistula (POPF), or in mortality rates or R0 resection rates between the two techniques [16–18]. In addition, laparoscopic DP was shown to be more cost-effective than open DP [19] and was associated with better postoperative quality of life than open DP [20].

The Dutch multi-center LEOPARD-1 RCT compared short-term outcomes of laparoscopic DP with those of open DP in patients with left-sided pancreatic tumors. The study enrolled a total of 108 patients, including 70 with neuroendocrine tumors and 43 with PDAC, and randomized them into two groups: laparoscopic ($n = 51$) and open ($n = 57$). The laparoscopic approach was associated with less estimated blood loss (150 mL compared with 400 mL; $P < 0.001$), longer operative time (217 min compared with 179 min; $P = 0.005$), a similar overall Clavien-Dindo ≥III complication rate (25% compared with 38%; $P = 0.21$), and a lower rate of delayed gastric emptying (6% compared with 29%; $P = 0.04$) compared with the open approach. The incidence rate of POPF grade B or C (39% compared with 23%; $P = 0.07$) was similar, and the need for percutaneous drainage placement did not differ between the laparoscopic and open groups (22% compared with 20%; $P = 0.77$), nor did the 90-day postoperative mortality rate (0% compared with 2%). The laparoscopic approach was associated with shorter time to functional recovery (4 days compared with 6 days; $P < 0.001$) and better quality of life from postoperative day 3 to day 30 compared with the open approach. The overall cost was similar between groups ($15,201 compared with $17,314; $P = 0.41$) [1].

Oncologic outcomes after resection for PDAC have been investigated by retrospective studies, which have reported similar oncologic outcomes between patients undergoing minimally invasive DP and open DP, although selection bias may have affected the results despite statistical adjustment [16, 17, 21–23]. The pan-European propensity score-matched DIPLOMA study, which enrolled a total of 1212 patients from 34 centers in 11 countries, resulting in 340 matched pairs, reported that minimally invasive (either laparoscopic or robotic) DP was associated with a higher R0 resection rate (67% compared with 58%; $P = 0.019$) and fewer harvested lymph nodes (14 compared with 22; $P < 0.001$) than open DP. Median overall survival did not differ between the two groups (28 months compared with 31 months; $P = 0.929$) [13]. Prospective studies comparing oncologic outcomes of minimally invasive DP and open DP are lacking, and future RCTs are warranted.

The robotic surgery platform may enhance the benefits of minimally invasive DP over laparoscopic DP. Meta-analyses reviewing the impact of robotic DP compared with conventional laparoscopic DP reported lower rates of conversion to open surgery and shorter hospital stays, as well as a higher rate of spleen preservation, in the robotic DP group. However, robotic DP was associated with a higher cost and a longer operative time (mean difference 28 min; 95% confidence interval 2–53 min) compared with laparoscopic DP. Other surgical outcomes such as POPF rate and overall morbidity did not differ between the two approaches [24, 25]. Oncologic outcomes have also been shown to not differ between laparoscopic and robotic DP [26–28]. Overall, both laparoscopic and robotic DP are safe and feasible options, and the choice of approach should be based on surgeons' preference and experience.

Minimally Invasive PD

PD is one of the most technically demanding procedures in gastrointestinal surgery, requiring precise dissection around vasculatures and high-risk anastomoses. The postoperative mortality rate for PD, which was between 20% and 40% during the 1970s [29], has significantly improved over time, dropping below 5% in high-volume centers in recent years [30–33]. Since the first laparoscopic PD was reported in 1994 [34], techniques for minimally invasive PD have continued to evolve [35, 36], most significantly with the emergence of the robotic surgery platform [37–40]. Meta-analyses have reported that minimally invasive PD is associated with less intraoperative blood loss and shorter hospital stays than open PD, with similar postoperative complication rates, including delayed gastric emptying and POPF [41–43].

Three RCTs, from India, Spain, and the Netherlands, have compared laparoscopic with open PD; results are summarized in Table 17.1 [2–4]. The RCTs from India and Spain were single-center studies, and all procedures were performed by one or two expert surgeons in both laparoscopic and open PD at each institution [2, 3]. These two trials consistently reported favorable outcomes with laparoscopic PD, with shorter hospital stays despite longer operative time, less blood loss, and lower overall complication rates compared with open PD. Similar lymph node harvests and margin status were also reported [2, 3]. However, the LEOPARD-2 trial conducted in the Netherlands, which was a multicenter national study that allowed only expert surgeons from four high-volume institutions who performed ≥20 laparoscopic PDs before entry, was terminated prematurely after accrual of 99 patients owing to safety concerns, with reported 10% 90-day mortality in the laparoscopic group compared with 2% in the open group [4]. The results of the LEOPARD-2 trial clearly demonstrate the safety concerns of laparoscopic PD, specifically the lack of generalizability of this technically demanding procedure.

Augmented surgical dexterity, particularly the wide range of instrument articulation provided by the robotic surgery platform, may improve the safety and generalizability of robotic PD [44–46]. Although no RCT has compared robotic PD with laparoscopic or open PD, several retrospective cohort studies have reported promising results [43, 47–52]. Studies using the pancreas-targeted American College of Surgeons National Surgical Quality Improvement Program and the National Cancer Database reported equivalent intra-operative and initial postoperative outcomes between robotic and laparoscopic PD, but the conversion rate to open PD was significantly lower in the robotic group [38, 53]. Zureikat et al. reported results of a multi-institutional study comparing perioperative outcomes of robotic PD with those of open PD using data collected from eight US institutions, including 211 robotic PD and 817 open PD. Robotic PD was associated with longer operative time, less blood loss, and lower major complication rates than open PD. No significant differences were seen in mortality rate, POPF rate, length of hospital stay, 90-day readmission rate, margin status, and number of harvested lymph nodes [50]. Similar results were reported in a propensity score-matched study using data from 17 international institutions [47]. These accumulating reports support the use of robotic minimally invasive PD; however, caveats are potential selection bias and the fact that most robotic PD procedures are performed by experienced surgeons at high-volume institutions. In addition, authors exclusively enrolled patients who underwent robotic PD administered by surgeons who had surpassed the learning curve, defined as 80 procedures [47, 50]. Moreover, oncologic outcomes after minimally invasive PD for PDAC are unknown. Prospective RCTs are warranted to determine the safety and non-inferior oncologic outcomes of robotic PD compared with open PD.

The biggest challenge in implementation of a robotic program for pancreatic surgery, particularly for PD, is its long learning curve. Even for conventional open PD, surgeons experience an

Table 17.1 Randomized controlled trials comparing outcomes between patients who underwent laparoscopic pancreatoduodenectomy (LPD) and those who underwent open pancreatoduodenectomy (OPD)

Reference	Country	Type of surgery	No.	Estimated blood loss, mL	Operative time, minutes	Clavien-Dindo grade ≥ III complications (%)	Postoperative pancreatic fistula (%)	Short-term mortality (%)	R0 resection (%)	Length of hospital stay, days
Palanivelu (2017)	India	OPD	32	401 (46)	320 (13)	12.5	18.8	3.1	93.8	13 (6–30)
		LPD	32	250 (22)	359 (14)	9.4	15.6	3.1	96.9	7 (5–52)
Poves (2018)	Spain	OPD	29	N.S.	365 (240–510)	37.9	31	6.9	51.7	17 (6–150)
		LPD	32	N.S.	460 (337–676)	12.5	31.2	0	59.4	13.5 (5–54)
van Hilst (2019)[a]	Netherlands	OPD	49	450 (300–1000)	274 (212–317)	39	24	2	76	11 (7–24)
		LPD	50	300 (200–438)	410 (252–481)	50	28	10	82	12 (721)

Values are expressed as mean (standard deviation) or median (range). *N.S.* not stated

[a]LEOPARD-2 multicenter trial, terminated prematurely owing to safety concerns

inherent learning curve that requires them to perform 60 procedures before achieving improved blood loss, operative time, length of hospital stay, and margin status [54]. Then, surgeons face a second learning curve when starting minimally invasive PD. Surgeons at the University of Pittsburgh Medical Center addressed this challenge by building a robotic pancreatectomy program with a robust training system [55–57]. They observed surgeon improvements in estimated blood loss and conversion to open surgery after 20 procedures, reduced incidence of POPF after 40 procedures, and improved operative time and number of harvested lymph nodes after 80 procedures; they concluded that 80 consecutive robotic PD procedures are required to overcome the learning curve [58, 59]. Others have reported a smaller number of procedures to reach proficiency in robotic PD [60, 61]. Institutions initiating robotic pancreatectomy programs are required to have robust pancreatic case volume and team commitment with high ethics, and they must carefully consider a logistic strategy to overcome the learning curve safely, making every effort to shorten the learning curve.

Foregut Robotic Surgery Program at MD Anderson

Our goals when we initiated our robotic foregut surgical oncology program at MD Anderson were to (1) ensure safety of the robotic procedures, (2) maintain the principle and quality of oncologic resection, and (3) minimize the number of patients required to get through the learning curve.

The volume–outcome relationship in complex gastrointestinal surgery, including pancreatic, esophageal, and gastric surgery, is widely reported [62–65]. The case-volume of a specific procedure for each surgeon or institution is the focus of most studies, but intuitively, experience with similar gastrointestinal procedures can accelerate the process of mastering a specific procedure. Busweiler et al. reported that hospitals with a "composite" case-volume (defined as the total number of cases including esophagectomies, gastrectomies, and pancreatectomies) of ≥40 per year had a higher lymph node yield, lower 30-day mortality, and better overall survival rates after gastric cancer resections than those with smaller case-volumes, although the numbers of gastrectomies of those "high-volume" hospitals were small (median of 14 cases per year) [66]. We therefore designed a combined program in which gastrectomies and pancreatectomies were both performed, effectively increasing the composite case volume of robotic foregut surgery and thus resulting in a shorter learning curve. The principles of oncologic lymph node dissection, necessary knowledge of surgical anatomy, and reconstruction techniques overlap between pancreatectomies and gastrectomies; experience and skills in robotic pancreatectomies and gastrectomies can thus be maximized synergistically in a combined program.

In addition to the effort to concentrate robotic foregut surgery experience, we encouraged a strategic approach with a stepwise increase of case complexity. Cholecystectomy is a good entering procedure to learn tissue dissection, and palliative gastrojejunostomy bypass is an ideal procedure to learn anastomotic techniques. DPs that require superior mesenteric vein (SMV) dissection and pancreatic neck tunneling must be experienced well before surgeons attempt PDs. Every procedural step of each procedure type should be thoroughly simulated and planned in advance. Observation of international experts in robotic gastrectomy and pancreatectomy, practice sessions with cadaver courses, and simulation of anastomotic procedures using biotissue were undertaken as a group. Preoperative detailed review of anatomy, including patterns of arterial/venous branches using high-quality contrast computed tomography images, is critical particularly in robotic pancreatectomies, where injury of these vessels and resultant bleeding can easily jeopardize the procedure. We are prospectively monitoring outcomes of robotic foregut procedures, which have been critically reviewed by the group to ensure safety, under a protocol approved by the Institutional Review Board.

The external retraction technique is a way to mitigate the limitations of the robotic surgery

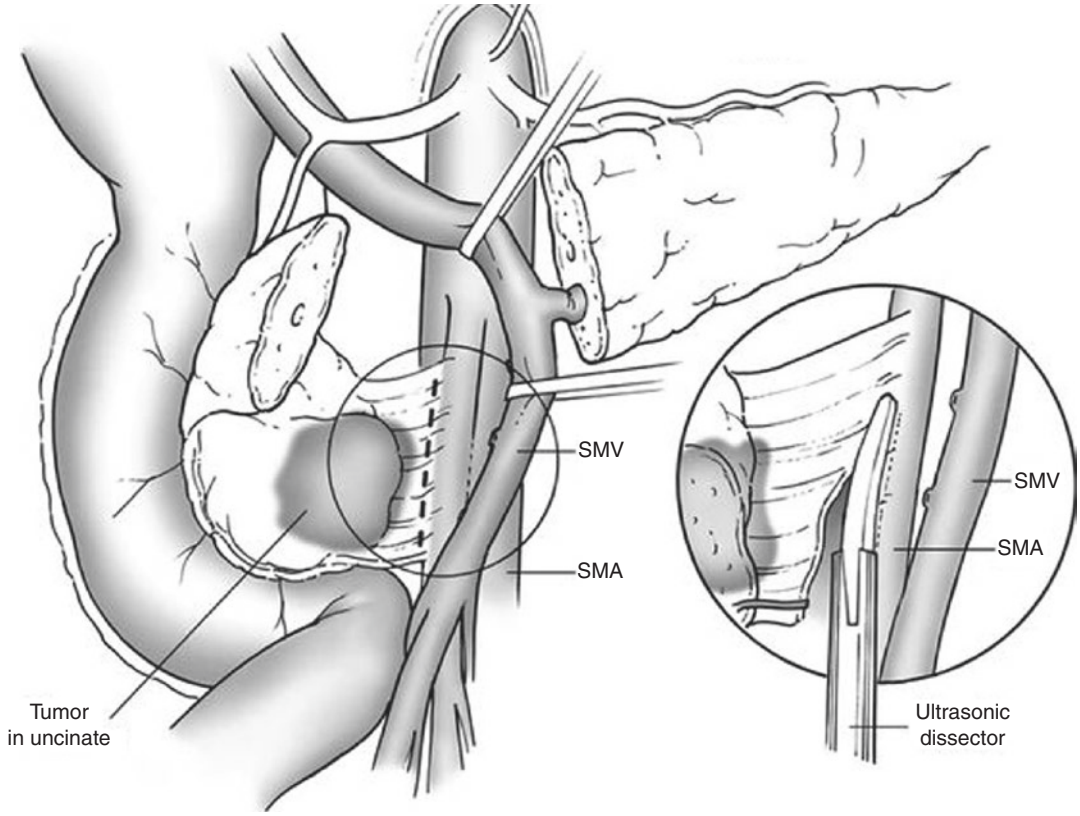

Fig. 17.1 Retraction of the superior mesenteric vein (SMV) to expose the superior mesenteric artery (SMA) is a critical step during pancreatoduodenectomy to improve the chances of R0 resection [67]. (With permissions from Matthew H.G. Katz)

platform and help maintain the quality of oncologic resection. Because of the current design of the robotic surgery platform, it is physically difficult for the surgical assistant to assist in exposing the cephalad aspect of the surgical field. SMV retraction to expose the SMA is a critical step during open PD. Given that the tumor edge often extends close to the SMA, SMV retraction and skeletonization of the right lateral aspect of the SMA is important to improve the chances of R0 resection (Fig. 17.1) [67], and this step should not be compromised in robotic PD. We developed a novel external retraction technique for the SMV. Vessel loops encircling the SMV are ligated with Endoloops, and the ends of the Endoloops are carefully retracted externally using a Carter-Thomason suture passer on the patient's left side (Fig. 17.2). This maneuver provides critical exposure of the SMA, which allows safe, high-quality oncologic dissection during robotic PD (Fig. 17.3).

Conclusion

Techniques and technology in minimally invasive pancreatectomy have been rapidly evolving. The safety of minimally invasive DP is established, and minimally invasive DP is well accepted as a standard approach for non-oncologic cases. However, the safety of minimally invasive PD is still a matter of controversy, and continued careful evaluation is warranted. Oncologic non-inferiority of minimally invasive pancreatectomy, in both DP and PD, needs to be evaluated in prospective trials. A minimally invasive pancreatec-

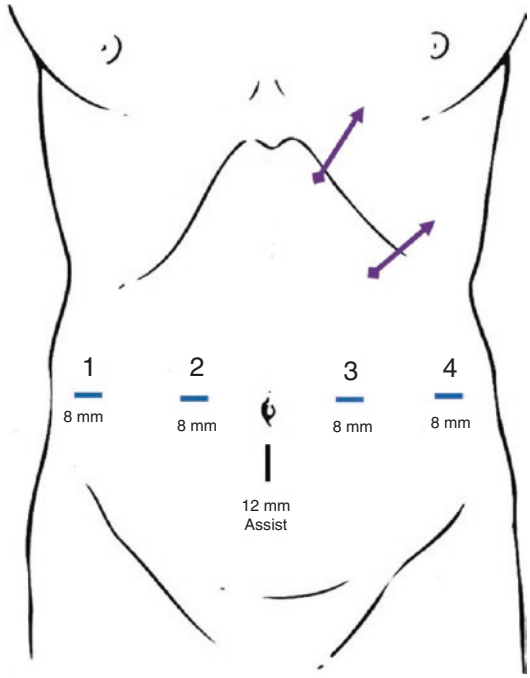

Fig. 17.2 External retraction site used for superior mesenteric vein retraction (arrows). Endoloop strings, which ligate vessel loops, are externally retracted using a suture passer and clamped at the skin level

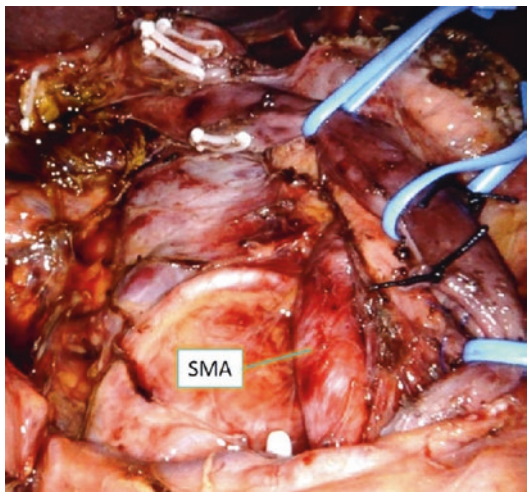

Fig. 17.3 Critical view of the superior mesenteric artery (SMA) provided by retraction of the superior mesenteric vein towards the patient's left

tomy program must be implemented with thoughtful strategic planning to ensure safety, and all effort should be made to shorten the learning curve.

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EUS-Guided Local Therapies

18

Ben S. Singh, Irina M. Cazacu, Adrian Saftoiu, and Manoop S. Bhutani

Introduction

Pancreatic adenocarcinoma (PDAC) is the most lethal and therapeutically resistant form of pancreatic cancer, representing 85% of all reported cases [1]. Current treatment options for these patients include systemic chemotherapy and radiotherapy [2, 3]. However, the prognosis continues to remain poor, with a median overall survival of <12 months and 5-year survival rate being approximately 10% [4, 5]. With only 20% of PDAC patients presenting at a resectable stage [6], significant improvements in treatment options and early detection programs are needed in order to increase the overall survival of our PDAC patients.

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The application of endoscopic ultrasound (EUS) in pancreatic cancer has risen over the last decades. This increase can be associated with the improvement of PDAC diagnosis that stems from the ability to accurately and dynamically visualize pancreatic malignancies with EUS. The further development of the electronic linear echoendoscope and the increase in size of the echoendoscope's working channels led to the expansion of roles that EUS could potentially play in PDAC [7]. The first line procedure for acquiring a cytopathological diagnosis for PDAC requires an EUS-guided fine needle aspiration procedure for direct tissue analysis [8]. This ability to safely and directly access pancreatic and other gastrointestinal tumors rapidly transformed the role of EUS to be an interventional procedure.

In recent years, EUS has gained increasing interest in the treatment of PDAC. Many clinical studies were performed to investigate the potential of EUS-guided direct injection of anti-tumor agents or EUS-guided brachytherapy for direct injection of radiation into pancreatic tumors. Furthermore, EUS interventions that have been studied in the context of PDAC treatments include EUS-guided radiofrequency ablation, cryothermal ablation, and microwave ablation to induce destruction of pancreatic malignant cells.

Over the last couple of decades, EUS application in the management of symptoms relating to PDAC such as pain, obstructive jaundice, and

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_18

gastric outlet obstruction has expanded. Many clinical studies have indicated that EUS-guided celiac plexus interventions such as celiac plexus neurolysis are effective for palliative care in patients with PDAC [9]. Moreover, patients with PDAC located in the head of the pancreas often present with bile duct obstruction and jaundice. In the case of a failed ERCP, EUS-guided biliary drainage has emerged as a great rescue alternative than surgery or percutaneous drainage because of its higher clinical success rate and safety profile [10]. Furthermore, EUS-guided gastrojejunostomy has emerged as another method for relieving gastric outlet obstruction. These EUS procedures are significant to note in the evolution of EUS's role in PDAC, however; the full description of these symptom management interventions is listed in other chapters. This chapter will focus on the recent applications and clinical data regarding interventional EUS in the treatment of pancreatic cancer.

EUS-Guided Fine Needle Injection of Anti-Tumor Agents

Pancreatic ductal adenocarcinoma (PDAC) is commonly characterized as a hypovascular tumor containing dense fibrotic stroma which commonly prevents adequate tumor cell penetration by systemic chemotherapy. As a result, EUS-guided fine needle injections of anti-tumor agents directly into the tumor has grown as a potential innovative method to treat PDAC. Furthermore, complications from systemic effects of chemotherapy and anti-tumor agents can potentially be minimized because of the direct access to the target tumor provided by EUS. These advantages have led to the interventional use of EUS in delivering anti-tumor agents for stromal-targeting therapy, guiding ablative therapies, and assisting radiation therapy.

EUS-guided delivery of anti-tumor therapies into pancreatic lesions has the potential to increase local drug concentration and reduce systemic exposure. Several EUS-guided anti-tumor agent injections have been performed with the goal of treating pancreatic cancer. To name a few, dendritic cells [11], oncolytic viruses (ONYX-015, HF10) [12, 13], cytoimplant (lymphocytic cultures) [14], and gene therapy (TNFerade, BC-819) [15, 16] have been injected under EUS guidance into pancreatic tumors. Oncolytic viruses like HF10 have been reported to have a strong anti-tumor effect and high tumor selectivity which has led to some promising clinical data in unresectable pancreatic cancer [17], metastatic melanoma [18], and metastatic breast cancer [16]. To date there are no randomized controlled trials to test and confirm the clinical benefit of these EUS – guided injections; however, phase I trials of these anti-tumor agents have shown the direct delivery of these agents in locally advanced pancreatic cancer (LAPC) patients to be safe and well-tolerated [11–13]. Two studies were able to show improved anti-tumor effectiveness when either Ad5-DS gene therapy or HF10 oncolytic viruses were injected in combination with systemic gemcitabine, suggesting a possible amplifying effect of stroma-targeting anti-tumor agent delivery [13, 19].

EUS-guided delivery of standard chemotherapy directly into a target pancreatic lesion has also been reported. The goal of intratumoral injection of chemotherapy would be to promote and increase local tumor toxicity which could allow for greater penetration of chemotherapy or even boost the radiation sensitivity within the tumor bed. Much of these studies involve animal models, specifically porcine models to test the feasibility and safety profile of direct injections of varying standard chemotherapies such as gemcitabine, irinotecan, and nab-paclitaxel [20, 21]. One prospective study involving EUS-guided direct injection of gemcitabine was performed in 36 patients with locally advanced and metastatic PDAC using a 22G FNA needle [22]. The procedure was seen to be safe and feasible for all patient with no initial or delayed adverse events reported. The study offered promising results in regards to tumor downstaging and overall impact on survival for these patients [22]; however, these promising results will need to be confirmed in further larger, randomized trials.

The growing interest in using molecular markers to determine a personalized treatment option

for pancreatic cancer has increased the number of clinical trials evaluating anti-KRAS agents to target specific PDAC mutations. Early phase I or II clinical trials are underway to test the delivery of several of these investigational KRAS inhibitors. The mechanism of action of these Anti-KRAS drugs is to prevent translation of KRAS proteins and even inhibit the growth of malignant cells overexpressing the KRAS mutation. One anti-KRAS agent that is being tested under EUS-guided delivery and is well-tolerated is siG12D LODER, which is a biodegradable polymeric matrix which holds si-RNAs for the specific mutated KRAS oncogene (KRASG12D) [23]. Theoretically, this anti-KRAS agent would inhibit translation of KRAS proteins and prevent the growth of malignant cells that express the mutated KRAS. Many of these novel studies are still focusing on safety and feasibility endpoints to see if the investigational drugs are tolerable in patients with PDAC. Current EUS-guided fine needle injections investigations for PDAC remains limited to safety and feasibility studies or smaller prospective case series. Multicenter randomized-control studies are needed to validate the clinical effectiveness of these EUS-injections for tumor downstaging, decreasing disease recurrence, and improving quality of life and survival of PDAC patients.

EUS-Assisted Radiotherapy

EUS-Guided Brachytherapy

One of the main goals of pancreatic cancer treatments is to achieve the conversion of tumor status to resectable for locally advanced pancreatic cancer patients. Unfortunately, downstaging of tumors with the current conventional treatment option still remains uncommon. There is some clinical data reporting that the use of brachytherapy in combination with standard chemotherapy can potentially increase the proportion of patients with LAPC that result in improved local control or that undergo surgical resection when compared with conventional treatments.

Through the direct delivery of radioactive microparticles or liquids, brachytherapy is able to deliver higher doses of radiation into target tumors [24]. This technique is currently being used as a clinical treatment of other malignancies (head and neck, liver, lung, cervix, or prostate cancer) [25–27]. Brachytherapy is heavily investigated for its potential use in cancer cell destruction because it is capable of delivering a higher and more precise dose of radiation when compared with conventional radiotherapy where radiation beams need to traverse healthy surrounding tissues to treat the malignant tumor, which can result in collateral radiotoxicity.

Combining the treatment of high dose radiation with the accuracy of high resolution EUS imaging can ensure a safe delivery of radioactive seeds directly into solid tumors. Unlike percutaneous implantation with CT or abdominal ultrasound guidance, EUS provides a clear direct puncture pathway with potentially lower complication rates. There have been several brachytherapy studies over the last century that have utilized a variety of different radionuclides, such as phosphorus-32, iodine, gold, iridium, and yttrium for pancreatic cancer patients [28–36]. However, much of these brachytherapy agents have limited clinical data and thus have not entered common clinical practice.

MD Anderson led the first United States multicenter experience with EUS-guided brachytherapy implantation of phosphorus-32 microparticles (P-32), in conjunction with standard chemotherapy in locally advanced PDAC patients was performed yielding promising results of tumor destruction [37, 38]. The OncoPaC-1 clinical trial tested the P-32 experimental device which carries the radioactive beta-emitter P-32 inside inactive silicon particles. It is implanted into solid pancreatic tumors under EUS guidance using a 22G needle, during the fourth or fifth week of the chemotherapy regimen [27]. The injection of P-32 is seen on EUS as an echogenic blush within the tumor (Fig. 18.1). EUS-guided brachytherapy implantation of P-32 yielded a local disease control rate of 88% with a median decrease in tumor volume of 9% (range +61 to −80%) 16 weeks

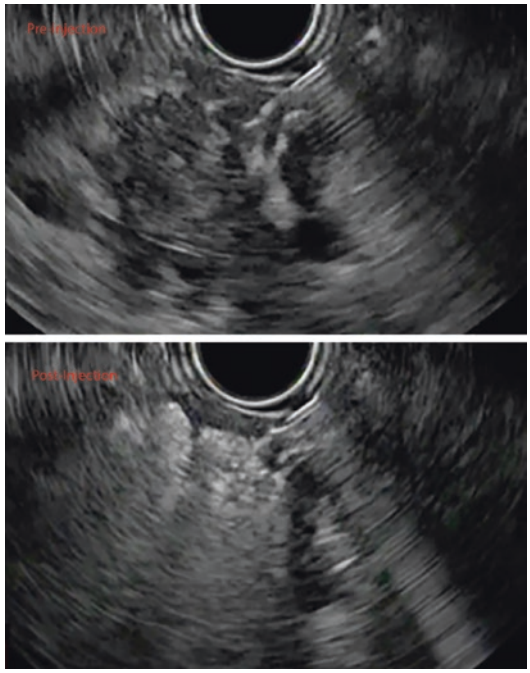

Fig. 18.1 Comparison of pancreatic head lesion on EUS before and after injection of P-32 microparticles. The injection is seen as a bright echogenic blush within the borders of the tumor

post-procedure [37]. Final results of this trial are pending. Another non-US clinical trial has shown great promise with EUS-guided P32 implantation for unresectable PDAC by reporting the successful downstaging and even surgical resection with some achieving an R0 resection [39]. The results from these pilot studies have shown that P-32 brachytherapy in conjunction with standard chemotherapy is technically feasible and has an acceptable safety profile in patients with unresectable PDAC. Preliminary data shows evidence of local disease control; however, further clinical trials are needed prior to EUS-brachytherapy to enter routine clinical practice.

EUS-Guided Fiducial Placement

The role of radiation in the management of pancreatic cancer is continuously evolving. PDAC is often attributed with high rates of local recurrence and distant metastatic disease. Improvements in distant control of pancreatic cancer have been obtained with multidrug chemotherapy regimens such as nab-paclitaxel plus gemcitabine and FOLFIRINOX [40, 41]. Thus, there is an increasing focus on local disease control, and radiation therapy is likely to become more important in this clinical setting.

Technological advances in radiation therapy including precision treatment planning and high dose delivery have allowed for the clinical application of stereotactic body radiation therapy (SBRT). SBRT has been seen to provide promising local control of gastrointestinal malignancies with acceptable rates of radiotoxicity to surrounding tissues [3]. This radiation modality is increasingly being used in oncologic treatments and is currently being investigated for application in locally advanced pancreatic cancer.

During the course of SBRT for pancreatic cancer, treatment planning with CT guidance from fiducial markers is needed for maximizing the radiation delivered to the target tumor [42]. Fiducial markers are metallic or liquid reference points that are implanted via EUS near or in the target solid tumor in order to map out the borders and radiation dosage that will be distributed to the surrounding normal tissue and target tumor [43]. The bright visualization of fiducials markers on CT imaging during treatment enables precise delivery through the evaluation of respiratory motion with respect to the real-time localization of the target tumor. In prior studies, fiducial markers were initially placed percutaneously with CT or ultrasound guidance or through surgical implantation [44]. In the past decade, EUS has evolved as the preferred method for placement of fiducial markers as it has the capability to provide excellent visualization of the pancreas and GI vasculature in order to avoid complications. Moreover, it allows for a shorter puncture pathway, which has been shown to be associated with a reduced chance of peritoneal seeding [45], thus overcoming some of the limitations of percutaneous injection.

Many types of fiducial markers and delivery systems have been developed and employed under EUS guidance [43]. Conventional fiducials

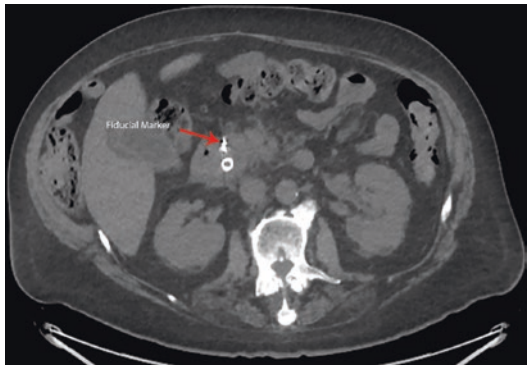

Fig. 18.2 Fiducial marker shown within the pancreatic tumor on CT-scan next to a biliary stent to help guide radiation treatment with SBRT

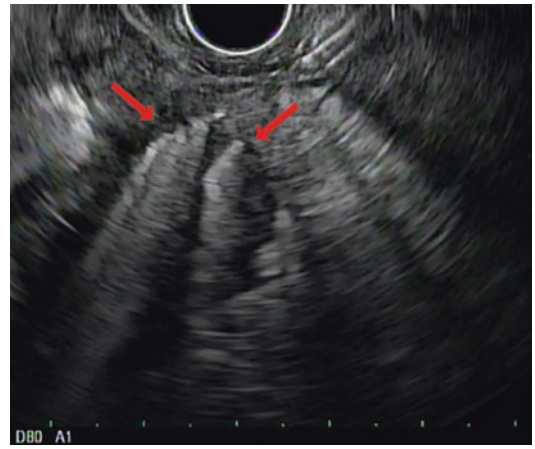

Fig. 18.3 EUS view of two fiducial markers placed in the center of a pancreatic head tumor indicated by arrows

are cylindrical gold seeds, 3–5 mm long and 0.75–1.2 mm in diameter and can be deployed using a 19G or 22G FNA needle, or a multi-fiducial delivery system [24]. Recent studies have provided a quantitative analysis of fiducial marker visibility and artifact production in order to determine the optimal fiducial marker for clinical use. The quality of fiducial visualization on cone beam CT is highly influenced by the brightness/contrast of the fiducial and the production of image artifacts [46] (Fig. 18.2). The recent study by Slagowski et al. compared the fiducial brightness and level of artifacts of numerous fiducial markers from many different vendors. According to the results, both contrast and artifact levels increased with fiducial diameter size. The maximum contrast was obtained for the large diameter (0.75 mm) platinum fiducials which were also associated with the highest levels of artifacts [47]. Minimum contrast and reduced artifacts were observed for the small-diameter (0.28 mm) gold fiducials. Balanced contrast and artifacts were noticed for gold fiducials with a 0.35- to 0.43-mm diameter, 5- to 10-mm length, and a coiled or cylindrical shape [46, 47].

The procedure for EUS-guided fiducial placement is similar to the technique of EUS-guided fine needle aspirations. Standard linear echoendoscopes are used for fiducial placement. It is critical to incorporate the color and power Doppler function of the echoendoscope in order to avoid major blood vessels that could be in the puncture pathway. For pancreatic solid tumors, it is recommended that at least three fiducial markers be placed in differing EUS viewing planes (Fig. 18.3) [24]. This helps the radiation oncologist to map out the best course of radiation distribution since the CT simulation and treatment planning occur in 3D viewing fields (Fig. 18.4).

EUS-guided placement of fiducial markers has been shown to be a safe and feasible procedure with high technical success rates [48]. Fiducial placement represents another application for interventional EUS and potentially expands the indications for SBRT by accessing anatomic structures that may have been otherwise inaccessible. Further clinical trials are needed to determine the optimal type of fiducial to be place under EUS-guidance and the survival benefits in patients with pancreatic cancer.

EUS-Guided Tumor Ablation

Tissue ablation has been used as a treatment for many different diseases including cardiac arrythmias and cancers [49–51]. Local ablative therapies can be performed under EUS guidance with the goal of causing intralesional tissue destruction and cellular necrosis. There is increasing interest for the potential of using EUS to guide ablative therapies for pancreatic cancer with the application of varying types of energies such as

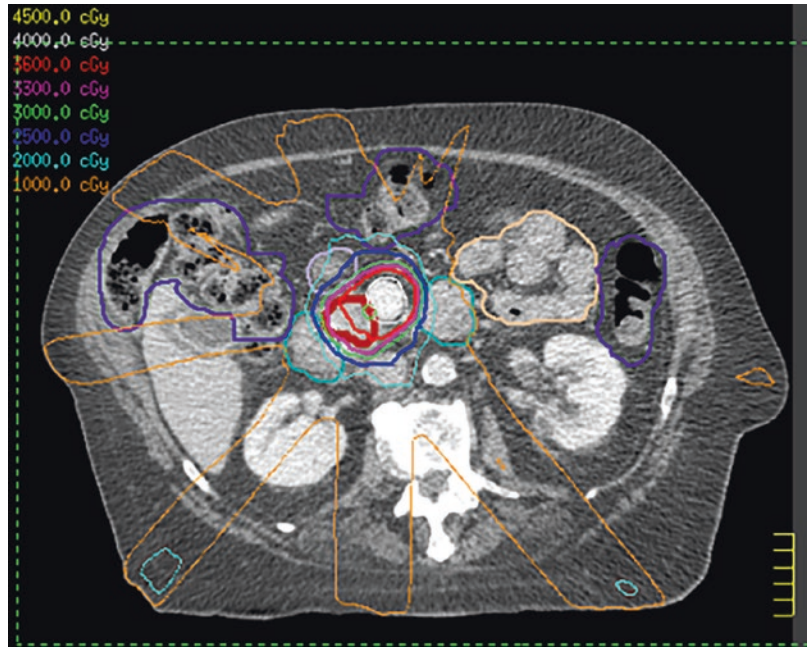

Fig. 18.4 Example of stereotactic body radiation therapy (SBRT) dose distribution planning based on fiducial marker location on CT-scan

microwave ablation, high-intensity-focused ultrasound (HIFU), cryothermal ablation, and radiofrequency ablation (RFA).

HIFU is a noninvasive ablative therapy that utilizes thermal denaturation induced by the ultrasound source to cause tumor necrosis [52]. There are mixed results regarding the use of HIFU in conjunction with chemotherapy, but there is promising results of observed durable relief of pain-related symptoms [53]. Results of HIFU treatments on PDAC are mixed, with this ablation method yielding some tumor size decrease with an overall size reduction rate of 50% [54, 55]. Multiple complications were reported such as transient pancreatitis, abdominal pain, and pseudocysts in these patients. Role of HIFU in treating PDAC is yet to be determined.

Even though RFA is well established in other clinical settings, its role in the treatment of pancreatic lesions is still under evaluation. According to several studies, percutaneous and laparoscopic RFA was seen to be feasible in patients with unresectable or locally advanced pancreatic cancer [56–58]. However, combining RFA with EUS can potentially offer a minimally invasive treatment option for pancreatic cancer. EUS-RFA is achieved by emitting energy from a RFA needle catheter, which can cause coagulative necrosis of the surrounding tumor tissue [59, 60]. Furthermore, combining chemotherapy or radiation therapy with RFA or any type of cryo-ablative therapy has been shown to potentially extend survival [61]. Follow-up studies regarding EUS-RFA had revealed increased blood supply surrounding the target RFA site confirmed by contrast enhanced-EUS, which can possibly lead to enhancing effects of systemic chemotherapy [62]. However, there has been some reluctance for endosonographers to use EUS-RFA in the patient setting for treatment of pancreatic cancer, because of the possible serious adverse events associated with RFA such as pancreatitis, peripancreatic edema, and burn injuries to the gastric wall [63]. Moreover, there is concern whether it is feasible to successfully ablate the total tumor volume within one procedure because of the classic diffuse margins seen on EUS with PDAC [64].

Multiple open-label clinical studies have reported positive data regarding feasibility and safety of EUS-guided RFA for treating locally advanced pancreatic cancer (LAPC). Song et al. reported the entire clinical experience of performing EUS-RFA in six human subjects to eval-

uate feasibility and safety. All six patients received conventional chemotherapy/chemoradiation for LAPC but with no overall reported benefit. All procedures were successful with no serious complications such as bleeding, pancreatitis, burns to the duodenal wall, or thrombosis of the portal or splenic vein. The pooled technical success rate for EUS-RFA procedures in pancreatic lesions was reported to be 100% with a pooled adverse event rate of 14.67% with the most common complication being pain [65]. During the EUS-RFA treatment process, multiple sessions of ablation periods may be needed in order to achieve the maximum destruction of tumor cells. Song et al. reported performing the procedure with 50 W of ablative power for 10 s in all patients [62]. There is currently no standard technical guideline regarding the optimal wattage setting and duration for adequate tumor destruction. However, the general recommendation for ablative power that has been reported in the literature ranges from 10 W to a max of 50 W depending on tumor size [64, 65]. Other studies have suggested that EUS-RFA can work better for pancreatic lesions if the ablation was applied with lower energy settings for a longer duration of time. In theory, this method should allow for greater but slower diffusion of ablative damage to the target tissue while also reducing the possibility of damaging the normal pancreatic parenchymal tissue [66, 67]. These studies suggested a moderate energy wattage of 30 W for a duration ranging from 15 to 95 s. Results based on the slower diffusion of ablation varied from showing complete resolution to a 50% reduction in size of pancreatic lesion.

The data on the long-term follow-up and clinical effects of EUS-RFA on PDAC is still limited. However, many studies like Song et al. did show a decrease in size of the pancreatic tumor on CT imaging 2–6 months post-RFA as evidenced by the presence of necrotic tissue within the lesion. Many of these patients show at best a partial response with reduction in tumor size during subsequent systemic chemotherapy or stable disease with no changes to the pancreatic lesion. The few studies that reported follow-up clinical measures, such as serum CA19-9 and CEA levels, did not show a significant change and only decreased in a small portion of the total patients. Overall, EUS-RFA has some promising results, but more clinical data and follow up studies are needed to determine the exact role of EUS-RFA in pancreatic adenocarcinoma.

EUS-RFA has also recently emerged for the management of other pancreatic neoplasms such as pancreatic neuroendocrine tumors (pNET) [57, 68]. There have been many recent studies describing the use of EUS-RFA for pancreatic neuroendocrine tumors (pNET) and pancreatic cystic lesions (PCL) for patients who are unfit for surgical resection [68, 69]. Similarly, it is still controversial whether asymptomatic non-functioning pNET less than 2 cm warrant the EUS-RFA procedure, [70–72]; and thus a multidisciplinary discussion should be conducted before attempting this technique. Overall, it is remarkable that the pooled overall effectiveness of EUS-RFA on pNETs was reported to be 96%, without any differentiations between functional and non-functional pNET [68].

There is growing interest in the possibility for EUS-RFA to be an adjuvant for inducing an immune response which could potentially target tumor antigens. The inflammation caused by the ablative thermal damage has been observed to cause an influx of T lymphocytes, natural killer cells, and dendritic cells at the target RFA site and systemic circulation within animal studies [73, 74]. Further studies looking into the immune response of RFA have evaluated the possibility of RFA-induced immunomodulatory effects to help enhance immunotherapies in patients with LAPC. This idea is still elementary; however, some studies have shown an associated activation of the adaptive immune response post-RFA which was measured by increased levels of both CD4 and CD8 T cells [75]. Likewise, a considerable increase in Effector Memory T cells which play a crucial role in the immediate memory response, confirms the ability of RFA to promote a systemic immune response. Immunotherapy drugs such as immune checkpoint inhibitors have not been seen to have a significant effect in treating pancreatic cancer; however, there is some potential that RFA can help induce a systemic

immune response to facilitate a stronger response to the immunotherapy. More clinical trials and data are needed to map the total immune response profile of EUS-RFA for patients with LAPC and to see whether combined immunomodulatory treatment by EUS RFA with systemic immunotherapy can enhance the effects of immunotherapy for patients with LAPC.

Conclusion

EUS has come a long way from being a purely diagnostic procedure. Interventional EUS techniques with the intent to treat pancreatic malignancies have shown great promise with the clinical evaluation of some of these procedures, with most showing adequate tolerance and acceptable safety. Although the initial results of many of these therapies are promising, many of these EUS-guided treatments need more investigative trials before their clinical effectiveness can be fully assessed in order to determine whether these therapies will have a routine role in the oncologic treatment of PDAC.

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19 Imaging-Based Biomarkers for Pancreatic Cancer

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Introduction: Different Contexts of Imaging for Pancreatic Cancer and How Imaging-Derived Biomarkers May Play a Role

The lethality of pancreatic cancer is due to multiple factors. Some of these factors include advanced stage at diagnosis, aggressive biology, and treatment resistance. Efforts to address each of these factors that influence the poor outcomes of the disease have been actively pursued for years, and some progress has been made. For example, early detection of the disease has been identified as a key priority area for patients with high risk of developing pancreatic cancer. Additionally, subtypes of the disease have been identified and may help achieve the goal of personalizing therapy. Through an improved understanding of the biology of the disease, strategies to overcome the therapeutic resistance to conventional therapies have emerged.

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In this chapter, we will highlight the clinical role of imaging for early detection, tumor characterization and stratification, and evaluation of treatment response. In each of these examples, imaging-based biomarkers will be described, and these quantitative imaging approaches may play a role in improving outcomes.

Considerations for Early Detection

The incidence of pancreatic cancer is 8 to 12 per 100,000, and there is a 1.3% lifetime risk of developing the disease [1]. Given the relatively low incidence, it is not feasible to perform general screening of the population because false positive rates with current diagnostic technology would be unacceptably high. The high false positive rate is due to the low specificity of diagnostic imaging to differentiate benign and malignant pancreatic lesions, while having relatively high sensitivity to detect abnormalities in the pancreas. In the case of pancreatic cancer, a false positive could have life-altering consequences for an individual, as other diagnostic tests and treatments for the disease can carry significant morbidity and have potential for procedure-related mortality. Indeed, overdiagnosis in certain patients with pancreatic cysts is a major conundrum for the healthcare community and patients that may lead to overtreatment [2]. Methods to increase the specificity of imaging

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_19

and derive new insights into the disease through characterization of the lesions may help address these challenges for early detection.

One way to increase the yield of screening efforts is to focus on patients with higher risk of developing pancreatic cancer than the general population and to use a sieve approach (Fig. 19.1). These high risk cohorts include those with known germline mutations that associate with pancreatic cancer [3–5], those with a family history of pancreatic cancer [2, 6], those with mucinous cystic neoplasms of the pancreas [7, 8], and those with new onset diabetes [9]. These high risk cohorts are discussed elsewhere in the book and have been reviewed previously [8, 10]. In each of these patient cohorts, diagnostic imaging tests may play an important role in surveillance or obtaining a biopsy of a suspicious lesion [8]. For each of the diagnostic imaging modalities, we review the clinical performance and indications for their use, as well as the prospects for quantitative assessment and extraction of features (or biomarkers) that may aid early detection efforts.

Prognostic Stratification of Tumors

For patients with an established diagnosis of pancreatic cancer, imaging plays a central role. Following a pancreatic protocol abdominal CT scan, clinicians can properly stage a pancreatic cancer. Despite the availability of TNM staging criteria, physicians generally rely on a clinical classification system based largely on the resectability of the tumor. We can classify pancreatic cancer along a continuum of potentially resectable to borderline resectable to locally advanced to metastatic. These general categories are discussed elsewhere in the book. Both the traditional TNM staging and the clinical classification demonstrate poorer prognosis with more advanced disease.

Ultimately, pancreatectomy is the only curative option for patients. Unfortunately, about 25% of patients who undergo laparotomy will have unresectable disease [11]. Conventional pre-surgical imaging is therefore imperfect in identifying resectable versus unresectable dis-

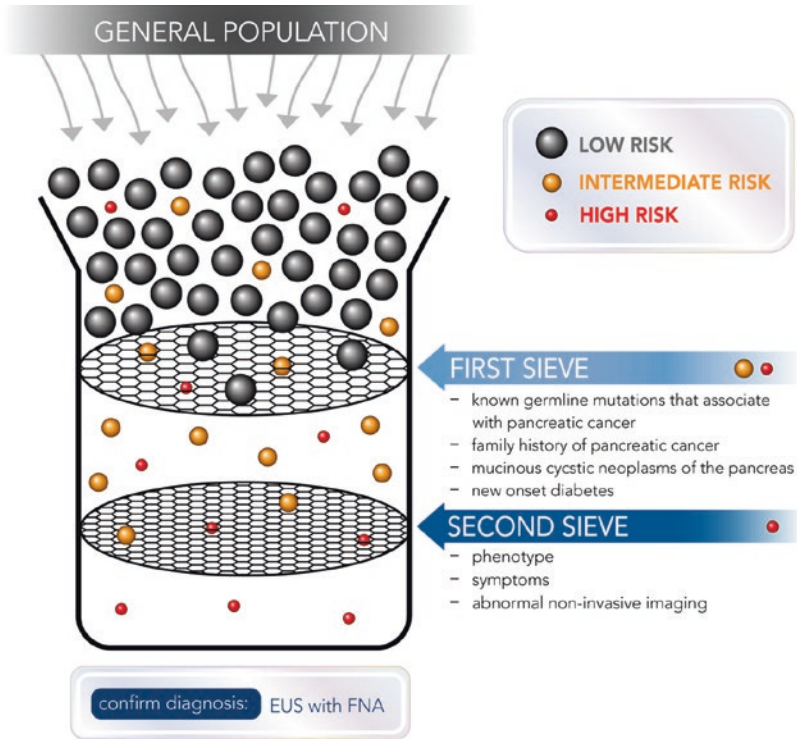

Fig. 19.1 Sieve Approach to Screening for Pancreatic Cancer. Modifications to the first and second sieve may occur with further research. For example, the second sieve may benefit from biomarkers derived from tissue, blood, urine, and imaging

ease. Helical CT scans have high predictive value for unresectability: the value ranges from 90% to 100% but is only 64–90% for resectability [12, 13]. A meta-analysis by Zhao et al. suggested that the sensitivity and specificity of multidetector CTs for detecting vascular invasion has increased in recent years, presumably because of improved technologies [14]. Tamburrino et al. performed a systematic review to assess the value of adding EUS to CT for determining resectability [15]. Ultimately, the study did not find any utility in the practice. Though imaging is limited in delineating resectability, staging laparoscopy seems to offer the greatest ability to detect small-volume metastatic disease. In fact, up to one-third of patients thought to be resectable on imaging will end up unresectable based on laparoscopic findings [16–18], highlighting the limitations of CT scans.

More recently, imaging has been revealed to have additional prognostic value beyond traditional staging. The use of radiomics and artificial intelligence has emerged as potential tools to help stratify patients by providing biological insight into the disease. We will discuss these tools in separate sections below on endoscopic ultrasound (EUS), CT, and MRI.

Treatment Response

The only biomarker that is Food and Drug Administration approved for pancreatic cancer is CA19-9. This biomarker is nonspecific, as benign processes and other malignancies may cause an elevation in the level. However, the degree of elevation of CA 19-9 (both at initial presentation and in the postoperative setting) is associated with long-term prognosis [19]. Among patients who appear to have potentially resectable pancreatic cancer, the magnitude of the preoperative CA 19-9 level can also help to predict the presence of radiographically occult metastatic disease, the likelihood of a complete (R0) resection, and long-term outcomes. CA 19-9 is likely to be much more elevated in unresectable compared to resectable disease (based on findings during surgery) despite appearance of resectability on CT [11].

The need for non-invasive, objective measurements of response for pancreatic cancer is important. Neoadjuvant chemotherapy is often offered to patients with borderline resectable and locally advanced unresectable pancreatic cancer. Studies indicate it is possible to downstage the disease with neoadjuvant chemotherapy, but this applies to a small proportion of patients [20, 21]. In the LAP07 study, which compared chemotherapy alone to chemotherapy followed by chemoradiation, only 4% of study participants who received neoadjuvant treatment of any kind were deemed suitable for subsequent resection [22]. A study of 257 stage III (unresectable) patients who underwent resection after neoadjuvant therapy demonstrated that 40% of patients could achieve either R0 or R1 resections and have similar survival rates as those with initially resectable cancer [23]. However, though some patients may be able to undergo R0 resections, recurrences are common [24, 25].

With cytotoxic therapies, it is relatively uncommon to see a reduction in size of primary pancreatic cancers, owing to the dense fibrotic stromal reaction in the tumor microenvironment. Indeed, size-based assessments of response for pancreatic cancer have proven to have limited prognostic utility [26]. The base rate of clinically meaningful pathologic response [27]after pre-op therapy is about 10% [6]. A study from MD Anderson in 2019 demonstrated that pathologic major response (pMR) or pathologic complete response improved survival compared to those with greater percentage of viable cancer cells in resected specimens following pre-op therapy [6]. Small median tumor diameter, lower rate of lymph node involvement, RECIST 1.1 partial response, and reduction in tumor volume were associated with pMR. However, attenuation/change in attenuation on imaging was not associated with pMR. Practically, the decision to proceed with resection after neoadjuvant therapy is generally based on the absence of disease progression rather than evidence of tumor response [6].

Specific Imaging Modalities

In the next sections, we discuss how endoscopic ultrasound, computed tomography, and magnetic resonance imaging (Fig. 19.2) are used on a routine clinical basis for pancreatic cancer. We also explain how quantitative biomarkers may be extracted from these imaging modalities to help in applications for early detection, tumor characterization and stratification, and treatment response.

Endoscopic Ultrasound {EUS}

EUS is largely regarded as the most sensitive method to detect cancer in the pancreas with sensitivity and specificity ranging from 70% to 90%, depending on T stage [28]. It has been shown to identify 2–3 mm lesions in the pancreas [29]. This resolution provides an advantage for EUS over CT and MRI in detection of small lesions.

The main indication for EUS in a patient with a pancreatic lesion is to obtain fine needle aspiration or biopsy material in patients suspected of having a pancreatic cancer. EUS is not a primary screening tool because it is not a readily accessible imaging modality and is highly dependent on the skill of the operator. Thus, in screening protocols for patients with high risk of pancreatic cancer developing, EUS is incorporated as a complementary method for imaging in conjunction with CT or MRI.

Future directions for EUS and quantification of the lesions include elastography, microbubbles, and confocal laser endomicroscopy. Given the high degree of fibrous stroma in the tumor microenvironment of pancreatic cancer, elastography demonstrates significantly lower values of elasticity for pancreatic cancer compared to normal pancreas (0.02% [95% CI, 0.01 to 0.02] vs

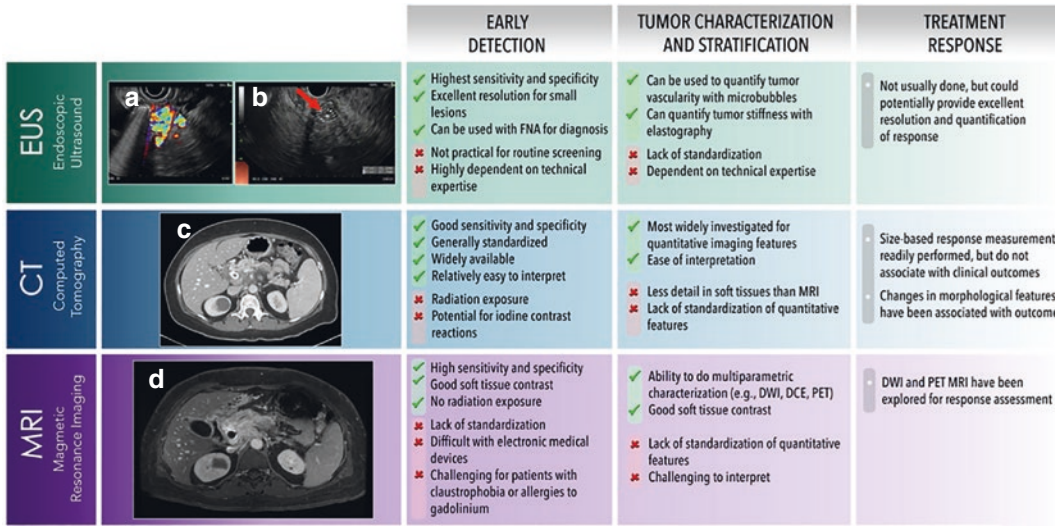

Fig. 19.2 Different Imaging Modalities for Pancreatic Cancer and Their Potential Roles. This is a 48 years old female who presented with painless jaundice and unintentional weight loss for a few months. A CT scan revealed an infiltrative mass in the pancreas and fine need aspiration indicated adenocarcinoma. She had stable disease after 4 months of modified FOLFIRINOX and underwent stereotactic body radiation therapy for consolidation of disease. (**a**) EUS with doppler images show collateral blood vessels overlying the tumor due to vascular invasion, and (**b**) the tumor adjacent to a mental stent (arrow). CT (**c**) and MRI (**d**) show the locally advanced tumor in the pancreas. The tumor caused occlusion of the superior mesenteric vein, an extensive thrombus in the main portal vein, encased the superior mesenteric artery, and had >180° involvement of the hepatic artery. These different types of imaging modalities play different roles in the diagnosis and follow up of patients with pancreatic cancer, and all can be used to extract quantitative information to help gain insight into disease biology and a patient's prognosis

0.53% [95% CI, 0.45 to 0.61]) [30], and this quantitative information about the behavior of the lesion can help improve performance. One study showed increases with EUS combined with elastography in sensitivity and specificity over traditional EUS [31]. The injection of contrast during the EUS procedure is another method to characterize the lesions. Density differences are required for EUS contrast to work, so microbubbles are the material of choice. The use of microbubbles during EUS provides a quantification of the degree of vascularity of the tumor. This measure associates with tumor biology such as the degree of differentiation of the tumors [32]. Here, the data with contrast enhanced EUS indicates a slightly higher sensitivity of 89% and specificity of 84% than historical performance of EUS alone [33]; direct comparisons and further validation would help to establish indications for microbubbles in the evaluation of pancreatic lesions. Finally, another advanced technique to characterize pancreatic lesions is confocal laser endomicroscopy. The technology has become compatible with EUS and provides a readout of the surface architecture of pancreatic cystic lesions. These surface readings have been associated with different types of pancreatic cysts, and a prospective study showed improved performance of confocal laser endomicroscopy over standard CEA and cytology analysis [34]. Moving forward, the incorporation of these advanced quantitative techniques is expected to improve the performance of EUS. However, there will be a need for overcoming the challenges of operator dependencies.

Computed Tomography (CT)

Contrast-enhanced multi-detector CT using thin axial sections with dual-phase pancreatic protocol acquisition (e.g., arterial and portal venous phase) is the standard of care for the evaluation of an individual who is suspected to have pancreatic cancer, and is routinely used for surveillance. The operating characteristics of CT allow for a reliable platform for fast imaging that has good spatial and temporal resolution [35]. However, the use of CT for individuals undergoing screening for pancreatic cancer, such as in high risk cohorts, is fairly limited due to the exposure of patients to ionizing radiation from the CT, potentially at a regular basis. For this particular reason along with the fact that imaging is done every 12 months for most screening protocols, CT is mostly used at the time a high risk individual is suspected to have pancreatic cancer. In general, CT has a sensitivity of 76% to 92% for diagnosing pancreatic cancer [36–38] and a specificity of 67% [36].

The underlying reason for the ability to identify pancreatic tumors on CT imaging is due to the differences between the vascularity of the tumor and surrounding pancreatic parenchyma in the majority of cases. This difference results in the characteristic hypodense lesion in the pancreas that is seen on a contrast-enhanced CT [39]. It is recognized that isoattenuating pancreatic tumors must be identified with other ways, such as differences in texture and secondary signs like a dilated pancreatic duct. These isoattenuating tumors with indistinct borders appear to have higher degree of stromal infiltrate and less aggressive biology compared to hypodense tumors with well-defined borders [40–42].

Indeed, data indicate that these morphological subtypes of pancreatic cancer, called high delta (well-defined borders due to high change in attenuation between tumor and parenchyma) and low delta (indistinct borders due to lack of difference in attenuation) are clinically relevant. This classification based on tumor morphology on CT scans can be quantified and has been associated with response to therapy, pathology such as in the stroma and immune infiltrates, genetic mutations, and survival outcomes in both retrospective and prospective studies [41, 43].

From a radiomics standpoint, the high and low delta pancreatic cancer classification is a semantic feature in that it can be visually described on baseline scans (Fig. 19.3). The classification can also be quantified in terms of the enhancement of the tumor, which is a feature known as the normalized area under the enhancement curve on CT [42]. This enhancement feature has been associated with survival outcomes as well, along with the delivery of gemcitabine, the degree of stromal

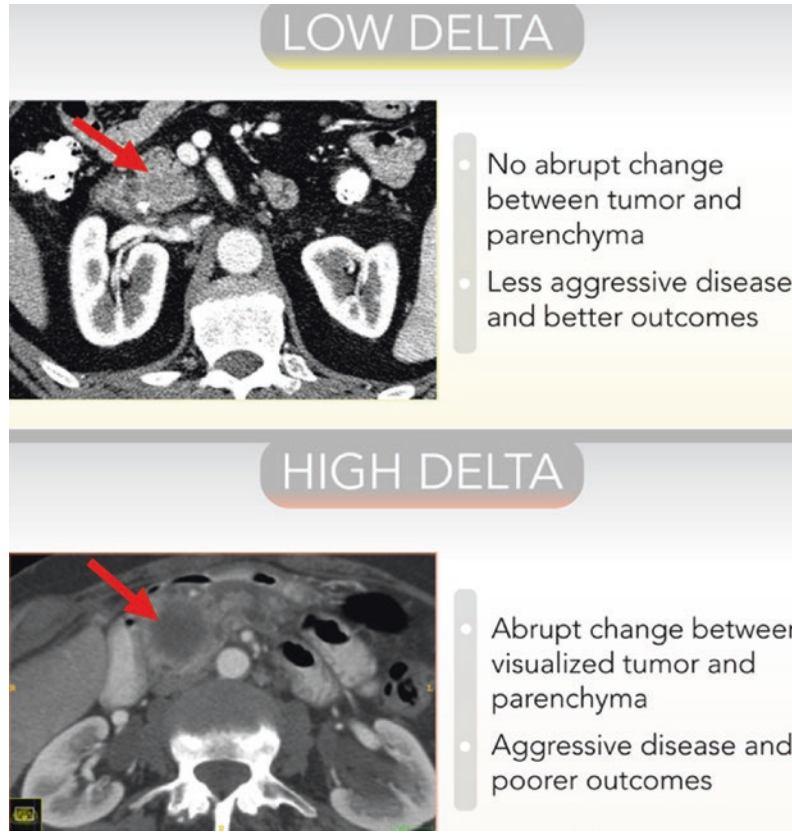

Fig. 19.3 Delta classification from computed tomography (CT) scans, showing a low-delta tumor without a distinct border (arrow, top) and a high-delta tumor with a distinct border (arrow, bottom)

infiltration in the tumor microenvironment, and treatment response. These results suggest that there are different imaging metrics (morphology, enhancement) that may characterize the biological and expected clinical course of pancreatic cancer.

As mentioned previously, studies have demonstrated that size-based radiographic response is not a great indicator of amenability to tumor resection after neoadjuvant therapy for neither locally advanced nor borderline resectable PDAC [44, 45]. Neoadjuvant chemotherapy may decrease the reliability of imaging to identify vascular involvement or change in tumor size. A small retrospective study from UCLA (University of California Los Angeles) demonstrated that CT and MRI scans done following neoadjuvant chemotherapy were only 71% sensitive and 58% specific to detect vascular involvement [46]. Moreover, this involvement was generally found intra-operatively to be nothing more than tumor fibrosis. Dense tumor stroma may prevent PDAC from shrinking [47]. Thus, we cannot necessarily correlate pathologic response and traditional size-based radiographic response [26, 48].

In 2018, Amer et al. described changes in the tumor-parenchyma interface on pancreatic protocol CT after neoadjuvant therapy [49] (Fig. 19.4). These changes were classified as either type I or type II responses. A type I response meant that the interface remained or became more defined whereas a type II response meant that the interface became less defined. Type I responders were significantly longer disease-free and had greater overall survival compared to Type II responders. In addition, patients with stage I or II PDAC who underwent neoadjuvant chemoradiation followed by surgery and were type I responders were more likely of achieving a major pathologic response.

Thus, there are two imaging-based features that may stratify pancreatic cancer: the baseline delta and the post-treatment interface response

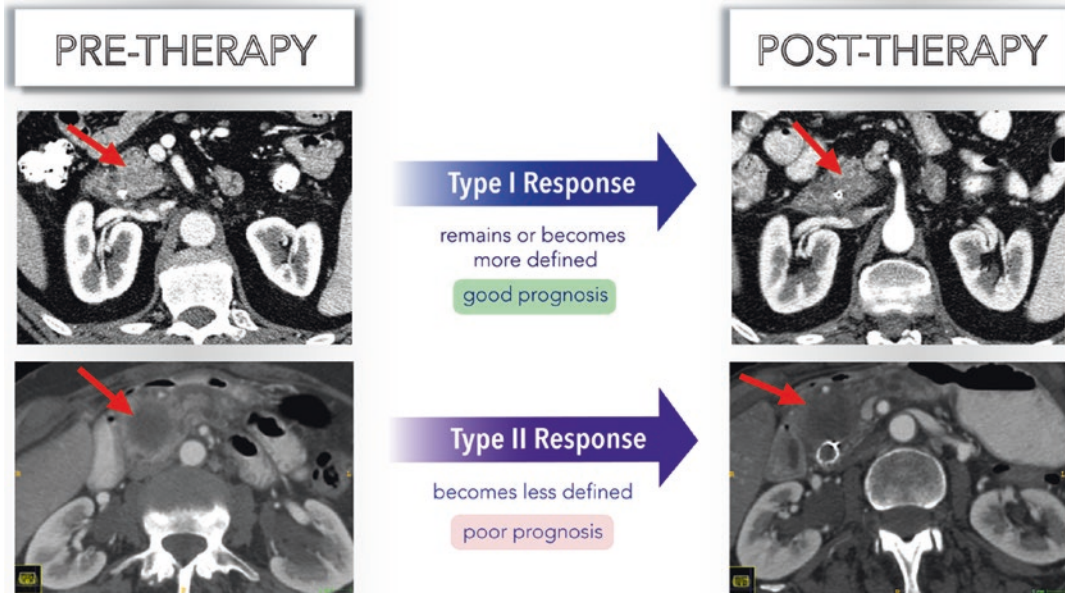

Fig. 19.4 CT scans showing type I interface response (top) and a type II interface response (bottom)

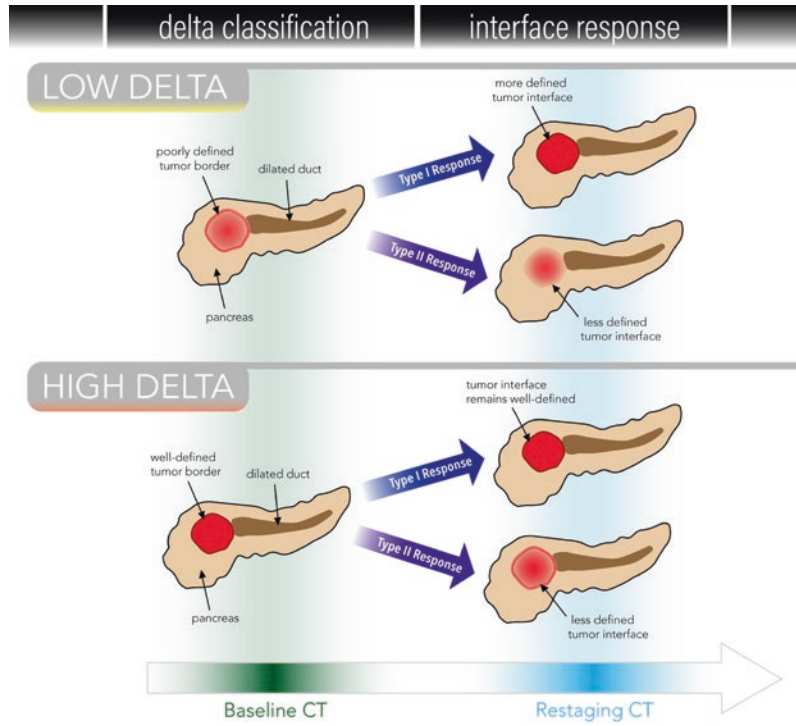

Fig. 19.5 Schematic illustrating interface response in low-delta and high-delta tumors

(Fig. 19.5). Most recently, a prospective trial validated the prognostic value of these two imaging-based biomarkers [43]. In this study, patients with high-delta PDAC were more likely to exhibit a type II interface response compared to those with a low-delta PDAC. In addition, patients with a type II interface response were more likely to have an R1 resection margin compared to those

who exhibited a type I response. Overall survival and progression free survival were greater in patients with resected (vs. nonresected) PDAC, low delta (vs. high delta), and type I response (vs. type II response). These findings may help personalize therapy for PDAC.

Additional features derived from CT include quantitative statistical measurements such as texture features. These represent traditional radiomics approaches. Researchers have used these radiomic features and lighting techniques with artificial intelligence (AI) to render three-dimensional images from standard of care CT scans [50]. These post-processing methods that help visualize differences in texture may help improve the detection of small pancreatic lesions. There are also potential applications of AI and radiomics for assessing tumor biology and treatment response. For example, texture has been investigated in the early identification of high-risk pancreatic lesions. Intraductal papillary mucinous neoplasms (IPMNs) are pre-malignant lesions which can possibly progress to pancreatic ductal adenocarcinoma (PDAC). Current consensus guidelines have high sensitivity in identifying IPMNs with high grade dysplasia, which are generally thought to be the lesions that require resection; the consensus guidelines have relatively low specificity, however, as many patients with IPMNs harboring only low grade dysplasia also undergo resection. Using quantitative imaging features, investigators demonstrated that high grade IPMNs have distinct physical properties on pancreatic protocol CT compared to the low grade subtype [51, 52]. The ability to measure texture features reproducibly across different institutions continues to be a major challenge, but these findings suggest there is promise in this work and further investigation is warranted.

MRI

Pancreas protocol MRI with contrast is another cross-sectional imaging modality that can be helpful in staging patients at initial presentation and for early detection screening protocols. Its advantages include that it does not rely on ionizing radiation for image acquisition and has better soft tissue resolution than CT. Disadvantages include the lack of standardization in the algorithms and parameters used to acquire advanced functional imaging sequences (e.g., diffusion weighted imaging [DWI], dynamic contrast enhancement [DCE]), susceptibility of the image quality to internal and external patient motion, cost relative to CT, and claustrophobia that some patients experience inside the machine. A pancreatic protocol MRI with contrast is the preferred imaging alternative to a pancreatic protocol CT if a patient has an iodine contrast allergy. Given the improved soft tissue resolution, MRI had better ability to detect pancreatic lesions than CT in a recent comparison study [53]. Indeed, in a screening protocol for patients with a genetic risk of developing pancreatic cancer, MRI was able to detect pancreatic lesions in 16 of 40 patients [54].

Diffusion-weighted MRI (DW-MRI) is a technique that depends on the molecular mobility of water and it is influenced by cellularity, stroma content, and vascularity of a given tissue. The different tissue parts are characterized by their own apparent diffusion coefficients (ADC) which reflect the level of freedom of water molecule movements.

DW-MRI may be helpful in evaluating treatment response in patients undergoing neoadjuvant chemoradiation. A study by Bali et al. in 2018 compared DW-MRI with RECIST for assessment of tumor response in patients with PDAC who underwent chemotherapy. They found that DW-volume and parameters derived from ADC maps allowed better patient categorization as responsive or not to therapy, especially early in treatment when modifications of the tumor microenvironment occur before overt morphologic changes [55]. Another study looking at patients receiving neoadjuvant chemoradiation found that changes between pre- and post-treatment ADC correlated with pathological response [56]. The value of ADCs may even go beyond the neoadjuvant setting. A recent retrospective study demonstrated that a lower pre-treatment ADC correlated with the presence or development of metastatic disease detectable on imaging. Furthermore, patients with lower pre-

treatment ADCs had significantly worse 4-year overall survival [57].

We may also be able to identify key differences in stromal composition and the modification to stroma in patients with PDAC [58]. As alluded to earlier, the tumor microenvironment of PDAC is a highly desmoplastic stroma that contributes to treatment resistance. Patients with non-differentiated and/or collagen-rich PDAC often have a poor prognosis. Dynamic contrast-enhanced MRI (DCE-MRI) is another imaging modality that can provide information about areas of hypoperfusion and is well-suited to the typically hypoperfused PDAC microenvironment. A 2016 pre-clinical study by Wegner et al. used DW-MRI and DCE-MRI to distinguish between collagen rich non-differentiated tumors and differentiated tumors with less collagen. ADC values of DW-MRI and total extravascular extracellular space (V_e) of DCE-MRI are two parameters that were found be higher in differentiated compared to non-differentiated PDAC models [59]. A later study by the same author suggested that DCE-MRI could provide further information about the tumor microenvironment as it relates to tumor hypoxia [60]. Intratumoral hypoxia is known to be a significant factor driving tumor resistance to cancer treatment. In fact, tumor stroma proliferation can be induced by hypoxia [61]. This hypoxia contributes to chemotherapy and radiation treatment resistance, and these imaging features may help identify patients for whom targeted approaches are warranted.

Emerging areas for MRI include the incorporation of elastography and positron emission tomography (PET). MR elastography (MRE) cannot have the sensor placed in as close proximity as EUS elastography. One solution to this problem is the use of an elastic belt to brace the upper abdomen, helping to better measure stiffness of the pancreas on 3.0 T MRE [62]. F^{18} fluorodeoxyglucose (FDG)-PET/MRI has been used for pancreatic cancer detection and assessment of treatment response. A major difference between PET/MRI and PET/CT is that the acquisition time for the PET signal with PET/MRI is significantly longer than PET/CT. This difference in acquisition time may result in higher yield in terms of FDG avidity on MRI for pancreatic cancer [63–65].

Artificial Intelligence

The emergence of artificial intelligence (AI) may aid the goal of early detection in multiple ways, including for imaging. Notably, AI may play an important role in early detection of PDAC by identifying not only the physical location of the primary tumor but also its secondary effects on the body. Toward identification of the primary tumor, Fishman and colleagues have described a radiomics-based machine learning algorithm to differentiate PDAC from benign conditions (i.e., normal pancreas and pancreatitis) with high specificity and sensitivity [50]. Combining AI-based approaches with other radiomics and quantitative imaging approaches may aid efforts to gain insight into the biology of the disease [2, 11, 13]. Such information may be applicable in terms of more personalized methods for screening of high risk cohorts for pancreatic cancer.

AI has also been useful for detecting secondary effects of pancreatic cancer on the body. For example, weight loss has been validated as one of three key factors to predict early stage disease in patients with new onset diabetes [66], and exocrine insufficiency appears to play an important role [67]. To identify these changes in weight, especially within specific body compartments like fat and muscle, researchers have fully automated imaging-based approaches and shown the relevance of this approach for pancreatic cancer [68]. For patients undergoing multiple imaging scans over time, the measurement of body compartments and detection of changes in these compartments could provide important metrics in the earlier detection of pancreatic cancer.

Future Applications

We can use other physical properties of PDAC, measurable via imaging, to personalize treatment. These properties require further research

before being targeted on a wide scale. There are differences in tumor vascularity that may provide a target for VEGF inhibitors. These may be useful for certain patients with markers of increased tumor-associated angiogenesis. This avenue has not yet been deeply explored [69–71]. Others have also targeted an integrin and developed a PET-tracer to $\alpha_v\beta_6$ for pancreatic cancer [72]. Moreover, there are opportunities to exploit tumor metabolism for differential effects on imaging studies. Early identification of patients with aggressive pre-malignant lesions can lead to more targeted therapy. The continued development of quantitative imaging-based biomarkers is essential to complement and support ongoing efforts to improve and personalize treatment for patients with pancreatic cancer.

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Liquid Biopsies in Pancreatic Cancer

20

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Introduction

Within the next decade, pancreatic cancer is estimated to become the second leading cause of cancer-related mortality [1]. Among pancreatic ductal adenocarcinoma (PDAC) of different stages, only patients with localized and primary PDAC harbor a potential for a cure. Surgical resection combined with adjuvant systemic chemotherapy is the main curative therapy for these patients [1]. Unfortunately, widely used screening techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) often do not detect resectable PDAC tumors [2]. Delayed diagnosis of PDAC due to the paucity of symptoms along with early dissemination of tumor cells to distant organs make less than 20% of primary tumors amenable to surgical resection at initial detection [3]. If a pancreatic mass is suspected by imaging techniques, aspiration of the mass can provide tissue samples needed for histological and molecular analyses.

Once tissue specimens obtained, genomic characterization of PDAC tumors may guide clinical decision-making [4]. Kirsten rat sarcoma oncogene homolog (*KRAS*) is the most prevalent mutated gene in pancreatic adenocarcinoma (~80–90% mutation rate) [5]. G12 in the *KRAS* gene is the most frequently mutated residue and responsible for ~97% of *KRAS* alterations in PDAC. Eight different substitutions at this position have been reported including G12D (51%), G12V (30%), G12R (12%), G12S (2%), G12A (2%), G12C (2%), and G12L/F (1%) [6, 7]. Other mutated residues Q61 (82% Q61H,

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_20

11% Q61R, and 7% Q61K) and G13 (76% G13D, 10% G13C, 10% G13S, and 4% G13P) are responsible for ~2% and ~1% of *KRAS* mutations, respectively [7]. *KRAS* is necessary for PDAC development as activating *KRAS* mutations are often followed by subsequent inactivation of tumor suppressor genes such as cyclin-dependent kinase inhibitor 2A (*CDKN2A*), tumor protein 53 (*TP53*), mothers against decapentaplegic homolog 4 (*SMAD4*), and breast cancer type 2 susceptibility protein (*BRCA2*) [8, 9]. A few other genes with recurrent somatic mutations identified in PDAC specimens are ring finger protein 43 (*RNF43*), AT-rich interaction domain 1A (*ARID1A*), transforming growth factor beta receptor 2 (*TGFβR2*), guanine nucleotide binding protein alpha stimulating (*GNAS*), RAS-responsive element binding protein 1 (*RREB1*), and polybromo-1 (*PBRM1*) [4, 9].

Traditional tumor biopsy often does not provide sufficient tissue specimens for molecular profiling after initial histology evaluation [10]. In addition to the potential need for an aggressive re-biopsy for further analyses, the risk of data misinterpretation for molecular profiling of pancreatic tumor samples is high due to the complex cellular composition of PDAC tumors, heterogeneity within the primary tumor, and potentially spatial heterogeneity between primary tumor and distant metastatic lesions [11]. Minimally invasive liquid biopsy approaches not only can facilitate prognosis and the early diagnosis of PDAC but also can dynamically monitor and manage the treatment response. These approaches mainly include the analysis of components that are released from primary tumors and metastatic lesions into blood including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and circulating tumor-derived extracellular vesicles (EVs) (Fig. 20.1a). With estimated half-life of 1–2.4 h for CTC [12], 16 min to 2.5 h for ctDNA [13], and less than 30 min for exosome in peripheral circulation [14], these actionable components in the realm of liquid biopsy have potential to dynamically capture pancreatic cancer initiation and evolution.

CTCs in Pancreatic Cancer

The presence of CTCs in the peripheral circulation of a cancer patient was reported for the first time in 1869 [15]. CTCs can be passively shed from the tumor mass or actively released from tumors into bloodstream in the course of metastasis [16]. CTCs size is between 9 and 30 micrometers (μm) and with blood capillaries diameter ranging from 3 to 8 μm, it would be expected that only small CTCs can keep circulating [17]. However, rare circulating tumor aggregates (≥ two cells) and white blood cells (WBCs)–CTCs clusters have been also captured in the bloodstream, with CTC clusters being more common in breast and lung cancers [18]. Such CTC clusters have a significantly increased metastatic potential but also a much shorter lifespan than isolated CTCs because of their interception by small blood vessels [19, 20]. CTCs are derived from both the primary and metastatic lesions and therefore, are highly heterogeneous that reflects the heterogeneity of the tumor(s) within a patient [21]. CTCs have been detected in the peripheral circulation in all stages of PDAC, whether localized, locally advanced, or metastatic [22]. CTC presence and count in pancreatic cancer patients has been widely ranged depending on the utilized enrichment and detection methods, blood source; portal vein blood (PVB) vs. peripheral blood (PB), PDAC type/stage, recurrence, and treatment response.

Several immunocapture-based and size-based technologies have been described for the enrichment of CTCs [23] (Fig. 20.1b). Currently, CellSearch is the only approved technology by the U.S. Food and Drug Administration (FDA) used in clinical trials studying the predictive value of CTCs [24]. CellSearch is an affinity-based technology using magnetic beads to eliminate leukocytes (CD45+ cells) and to enrich for circulating epithelial cells. Positive selection of epithelial cells is based on targeting surface antigens such as epithelial cell adhesion molecule (EpCAM), cytokeratins (CK) 8, 18 and/or 19 [25]. The CTC enrichment is then typically followed with a CTC detection step.

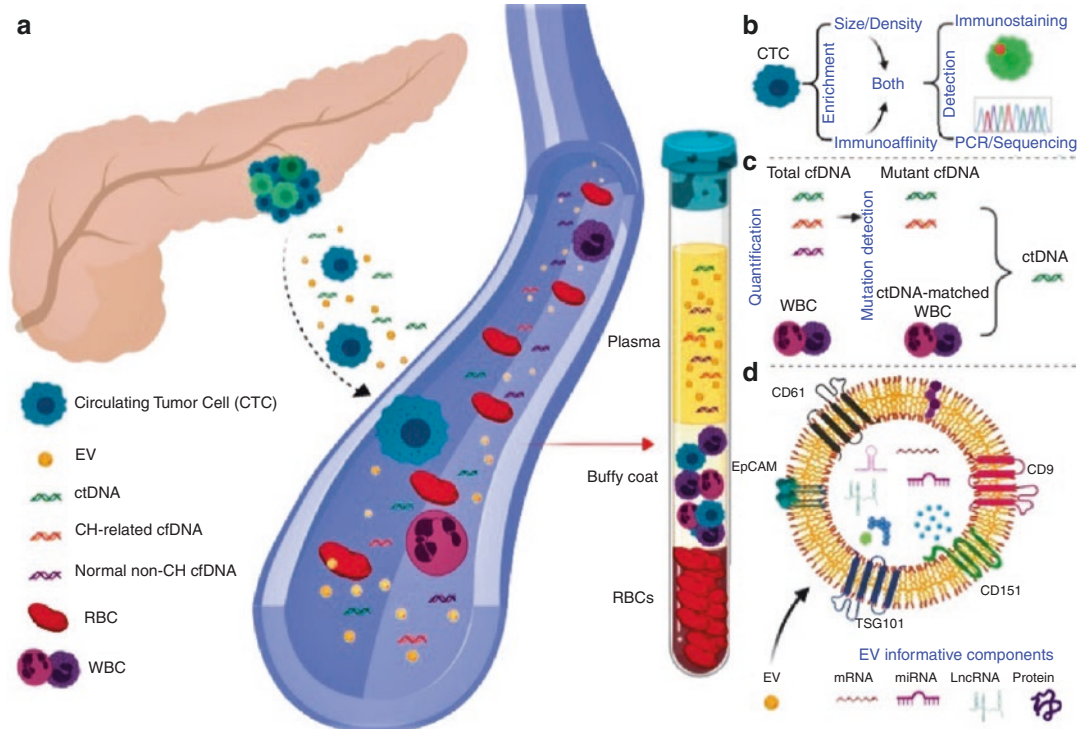

Fig. 20.1 Clinically relevant blood-derived biomarkers in pancreatic cancer. (**a**) CTCs, ctDNAs, and EVs are released from PDAC tumors into peripheral circulation and can be captured for further molecular analysis. (**b**) CTCs are actively or passively shed from tumors into bloodstream and can be isolated based on their size, phenotype or both. (**c**) ctDNAs shed by tumors comprises a fraction of the total cfDNA pool present in blood. Matched analysis of cfDNA and WBCs is necessary in order to distinguish ctDNAs from CH-related cfDNAs. (**d**) EVs are mainly released as a result of MVE fusion with the plasma membrane. EVs contain multiple biomarkers such as mRNAs, miRNAs, lncRNAs, and surface proteins. *PDAC* pancreatic ductal adenocarcinoma, *CTC* circulating tumor cells, *ctDNA* circulating tumor DNA, *EVs* extracellular vesicles, *cfDNA* cell-free DNA, *CH* hematopoietic clones, *WBCs* white blood cells, *MVE* multivesicular endosome

CellSearch was the first technology used to identify peripheral pancreatic tumor cells in 6 out of 16 (37%) metastatic PDAC patients [26]. Detection rate of peripheral CTCs using CellSearch in pancreatic cancer has been relatively low [27]. This might be due to the limitation of affinity-based CTC capture methods in distinguishing between tumor cells and nonmalignant cells. CTC selection in affinity-based approaches is based on the recognition of epithelial specific markers, predominantly EpCAM [28]. Although most pancreatic tumors are positive for EpCAM, not all tumor cells strongly express this protein [27]. Besides, during metastasis, EpCAM-positive tumor circulating cells may lose their surface epithelial markers as cells undergo epithelial-mesenchymal transition (EMT). Such CTC subpopulations with high metastatic potential might be circulating cancer mesenchymal-like cells that are potentially missed during the enrichment process [29].

Compared to affinity-dependent methods, size-based antigen-independent filtration devices such as isolation by size of tumor cells (ISET) have achieved more promising results with respect to both CTC detection rate and counts in PDAC patients (93% ISET vs 40% CellSearch) [27]. In an independent study using ISET, 78% of PDAC patients had CTCs expressing pan-cytokeratin and at least one of tumor initiating cell markers such as aldehyde dehydrogenase (ALDH), CD133, and CD44 [30]. The higher CTC positivity by ISET compared to CellSearch might be associated with the ability to select

CTCs of all phenotypes including epithelial, hybrid epithelial/mesenchymal, and mesenchymal phenotypes [31, 32]. However, this size-based technology may favor the enrichment of larger CTCs and exclude small CTCs of a particular origin [33]. Due to technology-driven biases in affinity-dependent and size-based methods, captured CTCs may not provide a snap-shot of the actual tumor heterogeneity [34]. Some most recent technologies take advantage of both immunoaffinity and size. Isolation of peripheral CTCs using a microfluidic platform (the "CTC-chip") by the interaction of CTCs with antibody (EpCAM)-coated microposts detected CTCs in 100% ($n = 15$) of PDAC patients [35]. Currently, due to the low-throughput rate of microfluidic platforms, such technologies cannot be used to analyze large sample volumes [36].

In addition to method-driven biases to capture pancreatic CTCs, the blood source for obtaining CTCs might affect their enumeration and characterization. In most studies, PB has been the main source of pancreatic CTCs. During the migration of tumor cells from the pancreas, CTCs flow along with the pancreatic blood stream through the portal vein into the liver [17]. Thus, physical restriction of hepatic capillaries traps large single CTCs and CTC clusters and reduces the detection success of CTCs in the peripheral circulation. In fact, CTC counts in portal vein of patients with pancreatic cancer are significantly higher than in peripheral circulation [26, 37]. Moreover, the high CTC counts in portal vein is correlated with intrahepatic metastases [26, 38]. For instance, at 3-year follow-up, a significantly higher rate of liver metastases were detected in PVB from CTC-positive versus CTC-negative resectable PDACs ($n = 20$, 53% vs 8%) [38]. This could help explain the common presence of intrahepatic metastases in pancreatic cancer patients [37, 39]. Despite the low detection rate of peripheral CTCs by CellSearch (10–50%), sampling from portal vein improved their detection rate up to 92% in early-stage PDAC patients who underwent curative resection (11 out 12 patients), suggesting that portal vein might be a better source to detect CTCs specially for early-stage PDAC patients [40]. In another study, CTCs were detected in PVB of all patients ($n = 18$; ~118.4 ± 36.8 CTCs/7.5 mL) versus only 4 matched PB (~22%; ~ 0.8 ± 0.4 CTCs/7.5 mL) [41]. Fourteen out of eighteen patients in this study were diagnosed with PDAC from which 7/14 were locally unresectable (6/7 with liver metastases) and 7/14 were borderline resectable PDAC. In a larger study with 41 PDAC patients, CTCs were detected in ~58% PVB samples compared to 40% of PB draws [37]. In most studies, PVB samples have been acquired in the intraoperative setting by the direct access to the portal vein which is not a realistic approach for repeated samplings. EUS-guided fine-needle aspiration (FNA), a minimally invasive percutaneous approach, can be used for EUS-guided portal vein sampling [42]. However, due to many reasons such as technical difficulties, and inadvertent injury, EUS-guided FNA for diagnostic purposes of PDAC has not become widely used for diagnostic purposes [43].

Detection method is another variable that can affect the interpretation of results (Fig. 20.1b). In addition to the CTC characterization by antibody-based immunostaining methods such as immunohistochemistry and immunofluorescence labeling, captured cells can be molecularly analyzed by technologies such as droplet digital PCR (ddPCR) and next-generation sequencing (NGS). ddPCR is a sensitive technique for the rapid detection and mutation allele frequency (MAF) quantification of well-known hotspots [34]. For example, using ddPCR, *KRAS* mutations in enriched CTCs were detected in ~72% of PDAC patients (42/58). This study also showed *KRAS* mutation status in CTCs is inconsistent with their matched solid tumor tissues in 42% of patients (11/26) [44]. It is now feasible to decipher genomic, epigenomic, transcriptomic, metabolomics, and proteomics landscape of CTCs by single cell analysis approaches to possibly manage precision medicine in every patient [45].

Longitudinal sampling of CTCs has shown prognostic value in PDAC patients. Analysis of peripheral baseline draws by CellSearch showed an 11% detection rate (cutoff of ≥1 CTC/7.5 mL) for locally advanced and 50% for metastatic PDAC [46]. Although reports regarding the association between CTC count and survival outcomes have been controversial, CTC positivity is associated with a trend toward poor survival. Detection of CTC in PDAC patients has been correlated with decreased overall survival (OS), worse progression free survival, and poor tumor differentiation [47–50]. Moreover, a higher number of CTC count has been correlated with the appearance of liver metastases in PDAC patients [38, 40]. However, one study did not confirm the observed correlation between CTC enumeration and survival outcomes (PDAC of all stages) or disease-free survival (DFS) in metastatic pancreatic cancer [32]. In addition, CTC detection in PB by CellSearch has been compared to other blood biomarkers such as mutant *KRAS* cfDNA. Analysis of varying $KRAS^{G12}$ mutations in 45 PDAC patients showed a higher sensitivity and better correlation with OS than CTC [51]. The average OS for *KRAS*-mutation positive cases was 60 days versus 772 days for *KRAS*-mutation negative patients while the average OS for CTC-positive and -negative were 88 days and 393 days, respectively [51].

Although CTC culturing and analysis techniques have dramatically improved, results should be cautiously interpreted. For example, not all enriched circulating cell might be clinically relevant, e.g. circulating epithelial cells associated with different benign inflammatory colon disorders are positively selected by current CTC enrichment methods [52]. Furthermore, CTC-like cells have been detected in some patients with benign pancreatic cystic lesions [53].

CTCs hold a great promise for the early detection, outcome prediction, and personalized treatment of many cancers including PDAC, even though challenges remain to isolate pancreatic CTCs with high sensitivity, specificity, and heterogeneous phenotypes.

Circulating Free DNA (cfDNA) and Circulating Tumor DNA (ctDNA)

Circulating free DNA (also known as cell-free DNA or cfDNA) refers to all fragmented extracellular DNA molecules circulating freely in the bloodstream [54]. cfDNA is mostly double-stranded and released either passively as the result of cell death (e.g. cellular apoptosis or necrosis) or actively by cell secretion, e.g. by exocytosis [54, 55]. In malignancies, ctDNA shed by primary tumors, metastatic lesions, and CTCs comprises a fraction of the total cfDNA pool in the peripheral circulation. The average total cfDNA concentration in cancer patients is about 180 ng/mL (ranging from 0 to 1000 ng/mL) and is higher than the average total amount of cfDNA in healthy individuals which is about 30 ng/mL (range of between 0 and 100 ng/mL) [56]. Therefore, theoretically, in patients with cancer, about 83% of total cfDNA in the blood circulation could be tumor-derived cfDNA (ctDNA). It should be noted that increased total cfDNA is not specific to cancer; e.g. elevated cfDNA has been reported in pregnant women, organ recipients or patients with non-malignant pathological disorders such as inflammation, autoimmune disease, diabetes, sepsis, acute myocardial infarction, and tissue trauma [57–59].

The first study on cfDNA in pancreatic cancer revealed that cfDNA concentrations in patients with carcinoma of the pancreas are significantly higher than both healthy individuals and pancreatitis patients [60]. The amount of ctDNA has been associated with a variety of factors including different cancer stages, metabolic tumor volume, and tumor histology [61]. For instance, lower amounts of tumor-derived cfDNA are detected in early-stage pancreatic cancer compared to locally advanced pancreatic cancer. As an example, in a cohort of 135 PDAC patients including 23% with resectable, 27% with locally advanced, and 50% with metastatic pancreatic adenocarcinoma, the average cfDNA concentration was 92 ng/mL (SD ± 201). The average cfDNA amount in patients with advanced PDAC (105.8 ± 227.25 ng/mL) was higher than in

patients with resectable tumors (52.5 ± 79.5 ng/mL) [62]. With cancer progression, the total cfDNA level is typically elevated as a result of increased ctDNA shed by dying tumor cells; e.g. because of the hypoxic conditions or immune response, and also cfDNA originated from normal immune cells involved in the antitumor response or normal cells in the tumor-surrounding tissue [59].

The high concentration of cfDNA in many cancers including PDAC is associated with decreased recurrence-free and overall survival (OS) [63, 64]. In pancreatic cancer, detectable ctDNA after resection has been correlated with disease relapse and poorer outcomes. Cancer recurrence through ctDNA surveillance could be detected several months earlier than with CT with an earlier prediction average of 6.5 months compare to CT imaging [65, 66].

Besides cfDNA concentration, fragment-size is also clinically relevant. Cells of the hematopoietic lineage are the predominant origin of cfDNA. Interestingly, cfDNA fragments of hematopoietic origin is longer in size than cfDNA from non-hematopoietic cells [64]. Consequently, the average cfDNA length in cancer patients, including PDAC patients, is significantly smaller than the average cfDNA fragment size in healthy individuals [64]. For example, the reported median cfDNA fragment-size by Agilent 2100 Bioanalyzer in healthy individuals was 176.5 bp (ranging 168–185 bp) while it was 170 bp (ranging 167–173 bp) in patients with locally advanced and 167 bp (ranging 148–180 bp) with locally advanced and metastatic [64]. The ratio of long to short DNA fragments to assess cfDNA integrity can be potentially used as a cancer biomarker [67]. It is possible to increase the fraction of ctDNA by selection of smaller cfDNA fragment sizes *in vitro* or *in silico* to improve the detection rate of ctDNA [68].

cfDNA quantification and fragment-size assessment are not the only strategies to analyze cfDNA. Numerous methods are now available to detect tumor-specific alterations including mutations, copy number alterations (CNAs), and aberrant DNA methylation for the detection and monitoring of cancer. Among genomic alterations, mutant *KRAS* is an excellent marker in PDAC due to its high prevalence in the disease (~90%), although not every patient will have detectable ctDNA. Detection of *KRAS* in cfDNA of PDAC patients goes back to 1994 when PCR was performed using allele-specific primers for amplification of mutant *KRAS* [69]. Nowadays, ddPCR is the most commonly used method for the detection of *KRAS* in cfDNA. Mutations in this gene were found in the circulation ~63% of PDAC patients (n = 75; all stages) and in 43% of early-stage pancreatic cancers (n = 51) [66, 70]. Patients carrying *KRAS* mutations had decreased OS compared to patients that do not. Detection rates varies across pancreatic cancer stages; e.g. mutations in ctDNA are reported in 34–46%, 31%, and 53–58%, of patients with localized, locally advanced, and metastatic PDAC, respectively [71, 72]. In another study, ~65% of patients (44/68) with metastatic PDAC had detectable ctDNA in comparison with ~17% of patients with locally advanced PDAC (6/36) [62]. The detection rate of *KRAS* mutations in cfDNA has been also significantly associated with reduced freedom from cancer recurrence and decreased OS [34]. Based on longitudinal studies, ctDNA detection; mainly measured by *KRAS* MAF, is correlated with worse progression-free survival (PFS) and also associated with the grade of pancreatic tumor differentiation; e.g. ctDNA was detected in 65%, 58%, and 30% of patients in cases of undifferentiated, moderately differentiated, and well-differentiated tumors correspondingly [62]. Thus, the quantitative monitoring of ctDNA in PDAC patients undergoing chemotherapy enables continuous evaluation of disease state [73].

ddPCR is unsuitable for the discovery of agnostic variants which can nowadays be achieved by NGS. For instance, in advanced PDAC patients with no detected G12 *KRAS* mutation, NGS revealed *KRAS* Q61K and *NRAS* Q61R variants [73]. In addition, a study carried out in 50 PDAC patients, ddPCR coupled with Ion Torrent targeted NGS identified several mutant cancer-related genes including 86% *KRAS*,46% *TP53*, 16% *SMAD4*, 4% *NRAS*, 2% *PIK3CA*, and 2% *STK11* (54% of patients with at least two mutations) [62].

One strategy to increase ctDNA detection sensitivity is to assign a unique molecular identifier (UMI) to each template molecule prior PCR amplification. This approach, named as Safe-Sequencing System (Safe-SeqS), enables reliable distinction between rare variants from technical errors [74]. PCR-based-SafeSeqS identified *KRAS* mutations (G12, G13, and Q61) in ~91% of PDAC tissue samples (38/42), and in ~62% (23/37) pre- and ~37% (13/35) post-operatively collected cfDNA samples [63].

ctDNA profiling can be also applied to monitor tumor burden in response to treatment. In advanced PDAC patients receiving first-line FOLFIRINOX chemotherapy, NGS identified at least one well-known driver gene alteration, including *KRAS, TP53, SMAD4,* and *CDKN2A,* in 65.8% of ctDNA samples derived from PDAC patients at baseline [75]. Mutant allele fraction (MAF) in ctDNA levels was correlated with tumor stage, metastatic burden, and OS. After chemotherapy, MAF of altered loci declined in chemotherapy-responding patients and increased in subjects with disease progression [75]. Of note, not all cfDNA with rare mutations in cancer patients are tumor-derived ctDNA. Normal hematopoietic stem and progenitor cells accumulate somatic alterations during aging which is known as clonal hematopoiesis (CH) [76]. The majority of cfDNA variants (reported as ~82% in healthy individuals and ~53% in cancer patients) originate from hematopoietic clones [76]. To avoid false-positive detection of variants due to CH, matched analysis of cfDNA and peripheral blood mononuclear cells (PBMCs) is necessary (Fig. 20.1c). For example, in a cohort of 66 PDAC patients with both cfDNA and tumor tissue samples, the concordance rates between these two were 52% for *KRAS* and 61% for *TP53* alterations [77]. There could be three main reasons for the dissimilarity between cfDNA and tumor mutation profiles. Tumor tissue specimens do not present the overall heterogeneity of the entire tumor(s), sequencing methods are not able to capture all mutations within the tumor tissue and cfDNA, and a portion of alterations in cfDNA samples originated from CH.

Recently, whole genome bisulfite sequencing (WGBS) of cfDNA interrogating methylation patterns demonstrates the potential to identify cancer and predict "tissue of origin" (TOO) [78]. Despite the high specificity (>99%) and predictive TOO accuracy of this method, sensitivity is still less than 50% in most stage I and II cancer types. Nonetheless, the average sensitivity in early-stage PDAC cancers is higher than the average sensitivity of all cancer types. The mean sensitivity of pancreatic cancer prediction in the validation cohort was 63% in early stage PDAC, 83% in stage II, 75% in stage III, and between 80 and 100% in stage IV [78].

Overall, these data suggest that ctDNA is a promising biomarker for primary diagnosis, therapy selection, and monitoring of treatment response; however, limitations related to the limit of detection of ctDNA still exist. This could be caused by the low abundance of ctDNA, specifically in early-stage and post-surgery samples, and the quality of fragmented cfDNA. Integrating advanced techniques such as targeted deep genomic sequencing of cfDNAs and matched PBMCs, use of UMI barcoding, and development of various error-correction methods, either computational or ex vivo (e.g. using the reactive oxygen species (ROS) scavenger hypotaurine in the case of lung cancer) might be necessary to circumvent these issues [61]. Furthermore, a combined analysis of cfDNA and CTCs sequencing could provide a more comprehensive genomic profile for cancer patients [79].

EVs

Extracellular entities, particularly EVs, are other blood-based analytes with potential clinical utility for PDAC patients. Diverse types of extracellular phospholipid bilayer-enclosed vesicles are circulating in body-fluids including small EVs (sEVs), microvesicles, and apoptotic vesicles [80]. Two of the most studied EV classes are sEVs (mainly exosomes) and microvesicles. sEVs typically have diameter size in the range of 40–150-nm (~100 nm), while microvesicles are

a lot more heterogeneous with 50 nm–1.0 μm diameter in size [81]. Exosomes are released as a result of multivesicular endosome (MVE) fusion with the plasma membrane [82]. Comparatively, microvesicles are shed from plasma membranes [81]. In addition to the biogenesis and size difference, sEVs and microvesicles differ in lipid composition and content [81]. Depending on the parent cell, EVs contain cellular components such as lipids, proteins, and nucleic acids [83] (Fig. 20.1d). Over the past years, exosomes have gained increasing interest because of their potential use in therapeutics and diagnostics. Numerous technologies and methods have been described for the enrichment of exosomes including isolation methods based on density (e.g. ultracentrifugation), size (e.g. chromatography), and affinity (e.g. antibody-coated magnetic beads) [34, 84]. However, sEVs are highly heterogeneous and routinely-used exosome isolation methods are not able to efficiently separate exosomes from other small EVs (sEVs) or small non-vesicular extracellular nanoparticles. Also, yield preparations of sEVs by these methods vary in heterogeneity and purity. In addition, specific markers are lacking to distinguish exosomes from non-exosomal subpopulations within sEVs [85].

One of the widely reported exosomal cargo has been double-stranded DNA (dsDNA) [86]. However, more recent work has shown that exosomes and other sEVs do not carry dsDNA and DNA-binding histones [85]. Therefore, dsDNA that has been reported to be present in cancer sEVs may have come from other extracellular non-vesicular (NV) compartments. NVs may contain dsDNAs through an MVE-dependent, but exosome-independent mechanism [85]. gDNA is embedded within the cell nucleus and is not accessible to multivesicular bodies (MVBs). It has been proposed that micronuclei (MN), which are extra-nuclear bodies resulting from chromosomal segregation errors, interact with MVBs [85, 87]. MN are more common in cancer cells with higher levels of genomic instability than in normal cells, and they are known to contain nuclear material including acentric chromosome fragments or whole chromosomes [87].

In EV-enriched yield preparations, it has been shown that not all gDNAs are confined within the extracellular entities. Treatment of extracellular entities by deoxyribonuclease (DNase) resulted in a reduction of approximately 50% of DNA [87]. In addition, extracellular entities seem to provide a protective shield against enzymatic degradation of gDNA. Concordance of both surgically resected primary pancreatic tumors and FNA-derived samples have been higher for eDNA (DNA from extracellular entities) than cfDNA (83–95% vs. 67–68%) [72]. In one study, ddPCR on eDNA samples detected *KRAS*^{G12D} and *TP53*^{R273H} mutations in, respectively, 40% and 4% of localized PDAC patients [76]. A higher rate of mutant *KRAS* in DNA from eDNA was detected than in cfDNA in PDAC patients. *KRAS* mutations were identified in 38–67% (eDNA) vs. 34–45% (cfDNA) in localized, 80% (eDNA) vs. 31% (cfDNA) in locally advanced, and 61–85% (eDNA) vs. 53–58% (cfDNA) in metastatic PDAC patients [71, 72]. Compared to cfDNA, eDNA also correlated better with PDAC progression (local → locally advanced → metastatic disease) [71]. In neoadjuvant-treated resectable PDAC patients, increase in *KRAS* MAF in eDNA correlated with disease progression while *KRAS* MAF in cfDNA did not. MAFs ≥5% at baseline status for both cfDNA and eDNA correlated with reduced PFS and OS [71, 72]. Based on a longitudinal study, MAF of eDNA significantly correlated with progression in metastatic PDAC in on-treatment serial samples while cfDNA MAF did not [71]. These results indicate that eDNA is a better prognostic biomarker that cfDNA for longitudinal monitoring of PDAC [71, 72].

Tumor-specific surface proteins in sEVs are other potential biomarkers for early detection of cancer that can be also exploited to separate normal from cancer-tissue derived EVs. Exosomes are enriched in canonical surface proteins such as tetraspanin family members CD63, CD9, and TSG101 [87, 88]. In addition to the common exosome markers, tumor-derived exosomes carry cancer-specific surface proteins [89]. Proteomic analysis of the exosome surfaceome (surface proteins) by chromatography-mass spectrometry

(MS) on 13 human PDAC cell lines revealed multiple PDAC specific biomarkers such as CLDN4, EpCAM, CD151, lectin galactoside-binding soluble 3 binding protein (LGALS3BP), and H2B clustered histone 21 (HIST2H2BE, and HIST2H2BF), many of them involved in PDAC initiation or progression [90]. Using a mixture of antibodies against these proteins, the authors enriched for PDAC-derived exosomes. This approach increased the detection of mutant *KRAS* from ~44% to 73% in patients undergoing active chemotherapeutic intervention [90]. In another study, it has been demonstrated that migration inhibitory factor (MIF) protein, a regulatory cytokine, is highly elevated in PDAC-derived exosomes and promotes premetastatic niche formation in the liver [91]. Therefore, exosome MIF might be another potential biomarker to predict liver metastasis and recurrence in PDAC patients [91]. Recently, PDAC-specific sEV-associated protein signatures were identified using a combination of MS and aptamer array-based proteomics. These sEVs were enriched for cancer-associated mechanistic regulators such as TP53, Myc proto-oncogene protein (MYC), KRAS, and cell proliferation/growth and immunoregulatory cytokines [92].

In addition to eDNA and EV-derived surface proteins, EV RNAs cargo are also potential biomarkers in cancer. Different types of RNA can be found in EVs including; messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), long non-coding RNA (lncRNA), microRNA (miRNA), piwi-interacting RNA, small nucleolar RNA (snoRNA), small nuclear RNA (snRNA), and Y RNA [93, 94]. Higher expressions of serum exosomal miR-17-5p and miR-21 have been reported in PDAC patients compared to the normal and chronic pancreatitis groups. Particularly, high levels of serum exosomal miR-17-5p have been significantly correlated with tumor differentiation and PDAC stage [95]. The use of combined EV biomarkers would likely increase the specificity of early PDAC diagnosis. Combined evaluation of protein and miRNA exosomal biomarkers (e.g. CD44v6, Tspan8, EpCAM, MET, and CD104) and PDAC-related miRNAs (e.g. miR-1246, miR-4644, miR-3976, and miR-4306) has been shown to be a promising tool in early PDAC diagnosis [96].

Despite the potential in diagnosis and monitoring significance of sEVs, the isolation and enrichment of pure cancer derived EVs remains a challenge. Conventional exosome isolation techniques are based on size and buoyant density [97]. Although Ultra-centrifugation (UC) is the most commonly used method for isolation of exosomes based on their size, it is time-consuming and labor-intensive with relatively low yield and purity [34]. Separation of sEVs based on their buoyant density by density gradient centrifugation is another method that could not outperform UC and is mainly useful for further purification of sEVs isolated by UC [97]. High-resolution iodixanol gradients can be employed to separate sEVs from NV components [85]. Sequential filtration comprising of sequential steps such as dead-end filtration, tangential-flow filtration, and track-etched membrane filtration is a potential approach to achieve a homogenous population of sEVs [98]. Tumor-associated sEVs enriched by size-dependent methods can be separated from non-tumor EVs using fluorescence-activated cell sorting (FACS) or affinity-based technologies like magnetic-activated cell sorting (MACS) [90, 99]. This requires targeting specific sEV-surface proteins to sort subpopulations of sEVs. Nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are examples of techniques that can be utilized to characterize isolated EVs [87]. Over the last few years, microfluidic techniques have been also incorporated for exosome isolation [100]. The major challenge using such techniques is unfavorable scaling of particles and their susceptibility for clogging their nanoscale channels. However, microfluidic methods might be a promising solution for sEV isolation with sufficient quality and quantity [101]. Furthermore, microfluidic platforms with tumor-specific antibody-coated surfaces like ^{EV}HB-CHIP could be used for isolation of cancer-specific EVs [102].

Among liquid biopsy biomarkers, extracellular entities (small extracellular vesicular and non-vesicular carriers) have a unique potential

because they possess numerous biological components. A combination of multiple biomarkers (e.g. dsDNA, mRNAs, miRNAs, lncRNAs, and surface proteins) will enhance their sensitivity and specificity for early detection of PDAC and improve disease monitoring by longitudinal measurements [83]. Besides, capturing tumor stromal cell-derived EVs such as EVs originated from immune, mesenchymal, epithelial, and endothelial cells, provide a significant amount of information on tumor complexity, growth, and immune response [83].

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Molecular Profiling and Precision Medicine for Pancreatic Cancer

21

Michael J. Pishvaian and Jonathan R. Brody

Introduction

Pancreatic cancer, and specifically pancreatic ductal adenocarcinoma (PDAC) is only the 11th most common cancer in the USA, and occurs in only ~5/100,000 people. Despite this, PDAC will soon be the second leading cause of cancer related death [1], and in 2022 is expected to cause 48,830 deaths [2]. A large part of the reason that PDAC is such a deadly disease is that diagnosis typically occurs at a later stage, and at least 50% of PDAC patients are diagnosed as metastatic and thus incurable from the outset [2]. Only 10–20% have resectable disease, with the remaining 30% being diagnosed with non-metastatic, and yet, unresectable disease.

However, the other major reason that PDAC is such a deadly disease is that we do not have particularly effective therapies. There is no question that systemic therapies have improved overall survival, with median overall survival (mOS) rates typically quoted as 8–11 months with the modern regimens of FOLFIRINOX and gemcitabine + nab-paclitaxel [3, 4], as compared to the prior standard of single agent gemcitabine, which was associated with a mOS of only 6–7 months [5]. Moreover, sequenced therapy in which patients receive second-line therapy is in large part responsible for mOS improving to 14–18 months [6], including in the control arms of recently presented Phase III trials [7, 8]. Moreover, whenever studied, more effective chemotherapy has been shown to help to maintain or improve the quality of life for PDAC patients [3, 4]. Therefore, it is important that all patients be evaluated and considered for systemic chemotherapy, and it is unacceptable that recent publications have suggested that over 50% of PDAC patients are not offered any therapy at all [9].

Nevertheless, the improvements in outcome, while statistically significant, and clinically meaningful, could still be considered only incremental, and there is a tremendous need for the identification of more effective, and personalized therapies. In this chapter, we will dispel the notion that PDACs do not harbor any "actionable" mutations (~25% of PDACs do harbor such mutations). We will discuss the specific actionable targets that have been identified in PDAC patients, and discuss the proven, and anecdotal data demonstrating benefit to treating PDAC patients according to their actionable findings. We will also highlight several still elusive targets, and discuss some of the efforts aimed at overcoming the prior barriers to therapy.

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_21

Sequencing Efforts Have Revealed Actionable Mutations

The first seminal effort to delineate, and classify the key mutations and associated pathways that are abnormal in a large cohort of PDACs with modern sequencing technology was by Jones et al, who evaluated over 100 pancreatic cancer samples for homozygous deletions and amplifications in the tumor DNA [10]. Since that time, there have been at least ten large scale sequencing efforts which together include tumors from well over 5000 individual PDAC patients [11–20]. The findings have been consistent throughout, that ~25% (Range 17–48%) of pancreatic cancer patients' tumors harbor actionable mutations, with "actionable" defined as pathogenic or presumed pathogenic mutations and/or gene fusions that are linked with, and have been shown to be predictors of response to specific therapies, albeit in any cancer type (see Fig. 21.1). In fact, it was this body of data that influenced the National Comprehensive Cancer Network (NCCN) to update their guidelines for pancreatic cancer patients in April, 2019, specifying that "tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon but actionable mutations [21]." These actionable mutations are being targeted in clinical trials in PDAC, and in many cases, as will be discussed below, offering appropriately targeted therapies to patients with actionable mutations has led to impressive outcomes, including disproportionate response rates, and survival times for a population of PDAC patients.

Best Examples to Date

BRCA1/2 (and PALB2)

DNA damage and chromosomal instability are hallmarks of cancer, and PDAC in particular, and in the last 15–20 years, it has become apparent that germline mutations in the Breast Cancer Associate genes 1 and 2 (*BRCA1/2*), as well as more recently the Partner and Localizer of *BRCA2* (*PALB2*) gene, can predispose patients to the development of PDAC. The gene products of *BRCA1/2* and *PALB2* play a critical role in the homologous recombination DNA damage repair (HR-DDR) process, the most error-free DNA repair mechanism, and loss of these proteins can lead to ineffective repair of double-stranded DNA breaks, resulting in an accumulation of mutations that can trigger carcinogenesis [22]. 3% to 5% of pancreatic cancers are associated with germline mutations in these genes [23]. Given the importance of the HR-DDR pathway in preventing chromosomal instability, it is not surprising that *BRCA1/2* and *PALB2* somatic mutations are also found in an additional 2%–5% of PDACs [14].

But the consequences of a defective HR-DDR pathway also present a therapeutic vulnerability in cancer cells that harbor these mutations.

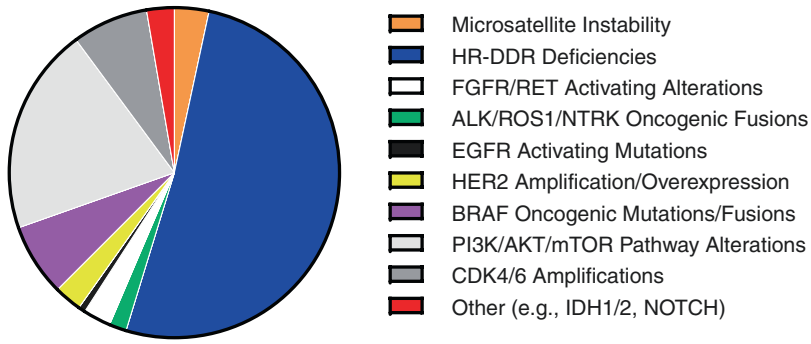

Fig. 21.1 Pie chart depicting the actionable signaling pathways disrupted in PDAC. The overall rate of actionable alterations was 26% in this publication. This pie chart demonstrates the frequency of actionable alterations within that 26%. (Extracted from Pishvaian et al. (Lancet Oncol. 2020 Mar 2))

Cancer cells that are HR-DDR deficient are particularly responsive to potent DNA damaging agents such platinum-based chemotherapy and/or poly(ADP-ribose) polymerase (PARP) inhibitors [24, 25], as the lack of efficient DNA repair results in unrepaired double stranded DNA breaks, leading to replication fork arrest, mitotic catastrophe, and cell death.

We and others have demonstrated that PDAC patients whose tumors harbor HR-DDR mutations have an improved mOS with platinum-based chemotherapy. Initially, Golan et al. evaluated the survival for 25 *BRCA1/2*-mutated PDAC patients who had undergone resection, and demonstrated an improved disease-free survival (DFS) for patients with *BRCA1/2*-mutated tumors who received platinum-based chemotherapy [26]. More recently, we were able to perform a large retrospective analysis of 820 PDAC patients. Patients were groups according the presence of an HR-DDR mutation vs. not; and whether they received any platinum-based therapy or not [25]. Importantly, in evaluating the patients who never received any platinum-based chemotherapy, it was apparent that the presence of an HR-DDR mutation was not in and of itself prognostically favorable, and if anything, outcomes trended towards being worse. Platinum-naive patients whose tumors harbored HR-DDR mutations had a mOS of 0.76 years compared to 1.13 years for DDR wild-type (DDR^{WT}) patients. By contrast, the presence of an HR-DDR mutation was strongly predictive of an improved outcome with platinum-based therapy. Platinum-treated patients whose tumors harbored HR-DDR mutations had a mOS of 2.37 years, compared to only 0.76 years for similar platinum-naïve patients, and compared to 1.45 years for platinum-treated, DDR^{WT} patients. Most recently, in a randomized Phase II trial of gemcitabine plus cisplatin with or without veliparib for germline *BRCA1/2/PALB2* PDAC patients, while the addition of veliparib did not improve outcomes, the mOS of both groups was 15+ months, establishing gemcitabine and cisplatin as a legitimate treatment option in this patient population [27].

The benefits of PARP inhibitors in *BRCA1/2*-mutated were first noted in a case series report by Lowery et al. who described 1 partial response (PR) and 3 stable diseases upon treatment with olaparib [28]. Subsequently, Kaufman et al. enrolled 23 *BRCA1/2*-mutated PDAC patients as part of a larger trial of olaparib in *BRCA1/2*-mutated cancers, and demonstrated a 22% objective response rate (ORR), including 1 complete response (CR) and 4 PRs [29]. Shroff et al. published their trial with 16 *BRCA1/2*-mutated PDAC patients treated with rucaparib, achieving a 16% ORR [30]. Importantly, Shroff's trial included patients with somatic-only *BRCA1/2* mutations, and at least one patient with a somatic only mutation had a CR on rucaparib—raising the possibility that PARP inhibitors might not need to be restricted to germline *BRCA1/2* mutation carriers only. Finally, the FDA recently approved olaparib as maintenance therapy based on the positive results of the randomized Phase III POLO trial, in which germline *BRCA1/2*–mutated PDAC patients, whose disease was stable on or responding to platinum-based chemotherapy, were randomized to olaparib vs. placebo [31]. The study met its primary endpoint, with olaparib improving progression free survival over placebo (7.4 vs. 3.8 months, $p = 0.004$). The olaparib results were supported by similar outcomes in a trial of maintenance rucaparib [32]. Thus, maintenance therapy with a PARP inhibitor is now a Level 1 treatment option for patients with germline *BRCA1/2* mutations.

Despite the excitement of the first targeted therapy ever approved for PDAC patients, there were also clearly patients that did not benefit from therapy. First, Shroff et al. described clearly that patients whose tumor were refractory to platinums (i.e. not just platinum "exposed" but their disease had grown while actively on platinum-based therapy), did not receive any benefit from rucaparib [30]. We and others have also demonstrated that in *BRCA2*-mutated PDAC patients treated with a PARP inhibitor, a secondary mutation that rescues the function of the BRCAs enzyme can lead to a loss of responsiveness to

PARP inhibitor-based therapy [30, 33]. Finally, there has been a growing appreciation that up to 1/3 of *BRCA1/2*-mutated PDAC patients exhibit innate resistance to platinums and PARP inhibitors, for reasons that are yet to be understood.

Nevertheless, the *BRCA1/2/PALB2*-mutated patients are the largest subgroup of PDAC patients to have received disproportionate benefit from targeted therapy thus far.

MSI-High

Pembrolizumab received FDA label indication for the treatment of MSI-high cancers of any type in 2016, and nivolumab was approved for the treatment of MSI-high CRC in 2017. These two anti-PD-1 agents serve to remove the immune checkpoints that cancer cells have harnessed to dampen the anti-cancer immune response, and have proven to be highly effective for tumors with high degree of microsatellite instability, and a resultant high tumor mutational burden, which is highly immunogenic. MSI-high PDAC is quite uncommon, with published rates of less than 1% [16]. Interestingly, in the Memorial Sloan Kettering experience, in which IMPACT tumor molecular profiling was accompanied by germline tumor testing, all of the MSI-high PDAC patients identified were found to have Lynch syndrome, with germline mutations in the MMR genes. Thus, somatic only development of MMR deficiency in PDAC appears to be very rare.

Pembrolizumab has been effective for MSI-high PDAC as well. Le et al. included six PDAC patients in their MSI-h pembrolizumab trial [34], and all patients had some degree of tumor reduction (4/6 had a RECIST criteria response). However, an update on this data by Marabelle et al. demonstrated, disappointingly, that in the 22 PDAC patients, the response rate for pembrolizumab was only 18%, and the responses were relatively short lived (relative to MSI-high tumors from other organs), with a median PFS of only 2.1 months, and a median duration of response (DOR) of 13.4 months (the DOR was unreached for all other highlighted disease cohorts) [35]. This highlights the need for effective combination therapies for MSI-high PDAC to extend the duration of response.

NTRK

The only other agents to receive FDA approval based on the molecular abnormality (and irrespective of disease type) are the TRK inhibitors, larotrectinib and entrectinib. Larotrectinib was FDA approved in 2018, and entrectinib in 2019 based on a very high degree of response (75%) [36]. Included in the larotrectinib trial was only one patient with PDAC, and that patient experienced a partial response. We had the opportunity to report two patients with NTRK fusion-positive PDAC treated with entrectinib, both of whom experienced some degree of benefit [37]. Thus, while identification of NTRK-fusion positive PDAC is a rare event, the disproportionate benefit of the TRK inhibitors, might well justify screening all PDAC patients.

Promising Targets

Other DDR Mutations

The DNA damage response and repair (DDR) pathway is a highly complex orchestrated system that exists to maintain the fidelity of the cell's original DNA sequence. While HR is critical for effective DNA repair, multiple other aspects of the DDR pathway are required for DNA repair. For example, the ATM and ATR proteins are essential for recognition of a DS-DNA break, and for coating the DNA strand for recognition for repair by the HR machinery. Cell cycle arrest is required to allow time for effective DNA repair. And alternative pathways of DNA repair exist, and are controlled by DNA-PK. We and others have shown that multiple germline and/or somatic mutations in the broader DDR pathway exist in PDAC, and, with *BRCA1/2/PALB2* mutations, 17–25% of all PDACs exhibit some DDR defect. What is unknown is the degree to which these Non-*BRCA/PALB* DDR mutations predict for a response to therapy.

As mentioned above, we have shown that patients whose tumors harbor DDR mutations broadly benefit from platinum-based therapy, as compared to non-platinum based therapy [25]. While our sample size was too small to compare *BRCA/PALB* DDR mutations to other DDR mutations, it was clear that the presence of any DDR mutation was associated with an improved survival with platinum-based therapy (compared to non-platinum-based therapy).

There are also early indications that the non-*BRCA/PALB* DDR mutations may be predictive of DDR inhibitors, outside of platinums and PARP inhibitors. For example, multiple studies have demonstrated that ATM-mutated tumors are more responsive to the combination of an ATR inhibitor and chemotherapy [38–43], and ATM mutations are among the most common DDR mutation identified in PDAC, occurring in ~6% of all PDAC patients.

KRAS Wild Type PDAC: Mutations in BRAF, and Other Receptor Tyrosine Kinases

The hallmark of PDACs is the presence of an activating *KRAS* mutation, which is found in 90–95% of all PDACs. Interesting recent work has strongly suggested that the *KRAS* G12R mutation, which is frequently found in PDAC (~20%) may have unique properties for both signaling and targeting [44]. These insights may provide personalized, targeted approaches for PDACs with specific *KRAS* mutations genotypes [45]. However, in the 5–10% of *KRAS* wild type tumors ($KRAS^{WT}$), other "drivers" exist, several of which are "targetable" with currently available therapies, either off label, or in the context of clinical trials.

For example, 4% of PDACs harbor a mutation in *BRAF*, at least half of which are the classically activating $BRAF^{V600E}$ mutation. A clinical trial targeting this specific subgroup of patients for treatment with the combination of the RAF inhibitor, encorafenib, and the MEK inhibitor, binimetinib has recently been initiated. But anecdotal data suggests that the combination may be effective for $BRAF^{V600E}$ mutated PDAC patients, with reports of PRs with treatment [14, 46]. In addition, other *BRAF* mutations may occur in PDAC, and these may exhibit sensitivity to other agents (Reviewed in Hendifar et al. manuscript submitted).

In addition, there have been reports of activating mutations, or fusions in genes that encode receptor tyrosine kinases. While only anecdotal data exist thus far, there have been case reports demonstrating significant benefit with appropriately targeted therapy. For example, Jones et al. identified that 3/47 (6%) of PDAC tumors were $KRAS^{WT}$, and all three harbored a fusion involving neuregulin 1 (NRG1), which is a HER3 ligand [47]. NRG1 activates HER3, resulting in receptor heterodimerization with other HER-family receptors, and leading to downstream signaling pathway activation. The NRG1 fusion gene results in persistent expression of NRG1, and thus continuous activation of HER3 [48]. Two of the three patients were treated with the pan-HER inhibitor, afatinib, and both benefitted with a significant and rapid response to therapy. One patient unfortunately experienced disease progression after 5.5 months, while the second was still responding at 5 months at the time of publication. A similar experience was published by Heining et al. in their 3/17 PDAC patients with NRG1 fusions [49].

Similarly, fusions in the ALK and ROS genes can occur in $KRAS^{WT}$ PDAC, and appropriately targeted therapy can lead to prolonged benefit. We published our experience with entrectinib in PDAC patients, 2 of whom harbored NTRK fusions. But one patient harbored a SLC4A4-ROS1 gene fusion, and started therapy with entrectinib [37]. He had disease control (stable disease) for nearly 7 months before progression. However, as proof of principle that his ROS1 fusion was a driving mutation, he then had prolonged disease control for more than 1 year on the second-generation ROS1 inhibitor, brigatinib (personal communication). Singhi et al. published the Foundation Medicine experience with sequencing over 3000 PDAC patients, and identified five patients with ALK gene rearrangements [50]. Four of the five patients were treated with

an ALK inhibitor, three of whom had prolonged stable disease (with one highlighted patient treated with ceritinib who had prolonged disease control for >17 months).

Overall, the actionability of molecular alterations in *KRAS*^{WT} PDAC patients can be significant. While the percentage of patients whose tumors harbor any one of these mutations is small, the therapeutic benefits can, again, be disproportionately beneficial.

Targeting the WNT Pathway: RNF43 Mutations and *RSPO2/3* Fusions

WNT pathway activation is triggered when neighboring cells secrete WNT proteins, in a process that requires the palmitoylation of WNT by the acyltransferase, porcupine [51]. Upon binding to co-receptors Frizzled and LRP5/6 on the target cell, WNT pathway activation involves a shift in the equilibrium between free β-catenin, and β -catenin destined for proteosomal degradation, leading to a greater cytosolic pool of free β-catenin, translocation to the nucleus, and interaction with TCF to mediate transcription of multiple oncogenic pathways [52, 53]. Wnt signaling has been known to play a key role in development and in cancer for more than two decades, and WNT pathway activation is well known to initiate tumor development [54, 55]. The canonical colon cancer carcinogenesis pathway is initiated by mutations in APC or β-catenin that allow for the constitutive activation of the downstream portion of the WNT signaling pathway [56]. Over the past two decades, a large body of research has shown that WNT signaling plays an important role in multiple cancer types, particularly in gastrointestinal cancers.

Recently, cancer genomic research has identified genetic alterations of proteins functioning in the upstream of the WNT pathway mutually exclusive from mutations in APC or β-catenin. For example, fusions in *R-spondin (rombospondin, RSPO), RSPO2* or *RSPO3*, can be found colon cancer [57]. RNF43, which is structurally related to ZNRF3, is a tumor suppressor, and negatively regulates WNT signaling by promoting degradation of the WNT receptor, Frizzled (while the activity of ZNRF3 is inhibited by the R-spondin proteins) [58–60]. Additionally, mutations in the RSPO co-receptor, *RNF43*, which is a tumor suppressor (and negative regulator of WNT signaling), can increase WNT pathway activation [61, 62]. Previous studies showed that inactivating mutations of *RNF43* frequently occur in premalignant lesions of pancreas, such as intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) [63–65]. In patients with pancreatic cancer, large scale sequencing efforts have demonstrated inactivating mutations in *RNF43* in 5–7% of pancreatic cancers [17, 66]. Occurrence of *RSPO3* fusions in pancreatic tumors has also been reported [67]. Notably, we and our collaborators have identified several pancreatic cancer patients carrying *RSPO3* fusions by using with whole transcriptome sequencing (unpublished). Although the frequency of *RSPO* fusions in pancreatic cancer patients is currently unknown and is expected to be low, its occurrence per se further supports the concept that WNT pathway activation at the upstream, independent of *APC* or *β-catenin* mutations which are rare in pancreatic cancer, plays a role in the development of a subset of pancreatic cancers.

There have been multiple attempts to block WNT pathway signaling for cancer therapy. Unfortunately, no WNT inhibitor drug has been successfully developed beyond clinical phase I studies despite significant efforts by the scientific community and pharmaceutical industry. Currently, the most promising approach to inhibit the WNT pathway is to prevent the paracrine or autocrine secretion of WNT proteins by blocking Pocn. Previously, it was demonstrated that WNT secretion can be blocked by a PORCN inhibitor [51]. Pre-clinical studies confirmed that PORCN inhibitor LGK974 resulted in the prevention of WNT palmitoylation, and thus a reduction in WNT secretion, which in turn inhibits tumors harboring mutations in *RNF43,* including *RNF43*-mutated pancreatic cancer xenograft models [62, 68]. LGK974 has entered in clinical

trials for the treatment of *RNF43*-mutated pancreatic cancer as a single-agent. More recently, novel PORCN inhibitors ETC-159 and CGX1321 have been shown to inhibit growth of tumors carrying RSPO fusions [69, 70]. Both ETC-159 and CGX1321 have entered in clinical trials for the treatment of GI cancers with *RSPO* fusion or *RNF43*-mutations as a single-agent.

Survival Benefit—A National Registry for Precision Medicine (the Know Your Tumor Program)

Despite national guidelines recommending molecular (genomic) testing for nearly all PDAC patients (those with advanced disease who are candidates for anti-cancer therapy [21]), there is still tremendous skepticism about the value of molecular testing, and a precision therapy approach. In that backdrop, we demonstrated that there is a survival benefit for patients with advanced PDAC who undergo tumor molecular profiling, and receive appropriately matched therapy [71]. Through a prospectively enrolled registry trial, PDAC patients were offered molecular profiling of their tumors. Based on the testing results, and their prior treatment history, patients were offered treatment options tailored to their molecular profile, which could include off label and clinical trial considerations. Over 25% of PDAC patient tumors harbored actionable alterations. Patients were then followed longitudinally, tracking the therapies they received, and for their longitudinal survival. In a retrospective analysis of over 1000 patients, those whose tumors harbored actionable molecular alterations and who received therapy appropriately matched to their molecular alteration (n = 46) lived 1 year longer than similar patients who did not receive appropriately matched therapy (n = 143; 2.58 years [95% CI 2.39 to not reached] vs. 1.51 years [1.33–1.87]; hazard ratio 0.42 [95% CI 0.26–0.68], p = 0.0004). Survival was also more than 1 year longer than patients whose tumors did not harbor any actionable molecular alteration (n = 488; 2.58 years [95% CI 2.39 to not reached] vs. 1.32 years [1.25–1.47]; HR 0.34 [95% CI 0.22–0.53], $p < 0.0001$). These data represent clearly, albeit through a retrospective analysis of a registry trial, the value of molecular profiling, and working towards access to appropriately matched therapy for PDAC patients.

Elusive Drivers

KRAS, TP53, CDKN2A/2B, and SMAD4

The classic molecular alterations in PDAC (and their associated percent prevalence [17, 18]), which are typically felt to be the drivers of pancreatic carcinogensis include KRAS (92%), TP53 (70%), CDKN2A/2B (35%), and SMAD4 (31%). Unfortunately, to date, none of these molecular alterations have been successfully therapeutically targeted. There have been no trials that have definitively targeted TP53 nor SMAD4 loss, and even trials of CDK4/6 inhibitors, while highly successful in, for example, breast cancer, and also with published promising pre-clinical data in PDAC [72] still have not demonstrated that the presence of a CDKN2A/2B mutation is at all predictive of a response to therapy. KRAS in particular has been extensively studied, but early attempts to target farnesylation, and thus, in theory anchoring of KRAS into the membrane were unsuccessful. More recently, several groups have looked at targeting signaling pathways downstream of KRAS, but trials of single agent MEK inhibitors have not improved outcomes, not even when combined with chemotherapy [73]. Several trials targeting two downstream pathways are ongoing, and there has been some initial promise of combining a MEK inhibitor with an autophagy inhibitor—but these trials are still very preliminary. The most promising recent KRAS targeted strategy has been targeting the $KRAS^{G12C}$ mutation specifically. AMG 510 (Amgen) can induce responses in patients whose tumors harbor a $KRAS^{G12C}$ mutation [74], which occur more frequently in non-small cell lung cancer and colorectal cancer. Unfortunately, this specific mutation is only found in <1% of PDACs.

Immunotherapy

Clinical trials of single agent immune checkpoint inhibitors, and even combination of, for example, anti-PD-1/PD-L1 inhibitors plus CTLA-4 inhibitors have been largely unsuccessful for PDAC. The one exception is for patients with mismatch repair deficient PDAC (microsatellite high), where 4/6 patients with MSI-H PDAC responded to therapy [34]. Unfortunately, these mutations are quite rare, occurring in <1% of PDACs. Furthermore, in a recent update, the median PFS was only 2.1 months—far less than the PFS and OS in other MSI-H disease types [35]. Nevertheless, this is a window of opportunity for combination trials to illicit a greater durability of response in this rare PDAC patient population.

Future Directions: Other Considerations and Biomarker Driven Approaches

Others have applied high throughput sequencing and RNA analysis to subtyping and classifying PDACs into categories that presumably will aid in tailoring therapies (for a review of this work please refer to [75]; these sub-categories include classical, immunogenic, and squamous type PDACs. More recent, sophisticated studies are consistently refining subtypes and attempting to classify PDAC tumors [76–78]. As better therapies emerge and we further identify facile methods to classify these tumors, this subtyping work should add value to precision therapy based trials for PDAC. Other important elements of the PDAC tumor that are being exploited and explored is the critical tumor microenvironment that surrounds the epithelial PDAC cells. Not only could the amount of stroma content, but the elements in the microenvironment such as low glucose and hypoxia [79, 80] could dramatically disrupt the efficacy of targeted and non-targeted therapeutic strategies. Being able to rigorously quantitate these elements in the tumor microenvironment may factor in our decision making for choosing certain therapies (e.g., immunotherapies and therapies targeting the metabolic milieu of the tumor).

Finally, the future of precision medicine may incorporate both serial biopsies, liquid biopsies, and development of patient derived models of cancer (PDMCs); which could all be used as companion diagnostics to guide and adjust therapies to patients in real time (Fig. 21.2). For example, our best targeted strategies typically only extend OS, and unfortunately, many PDACs either ultimately become resistant or an emerging resistant clone emerges that kills the patient. By developing and validating PDMCs and a liquid biopsy strategy, we may be able to detect emerging clones sooner, and at the same time, use PDMCs to predict what therapies to pivot to in an effort to break acquired resistance mechanisms (Fig. 21.2).

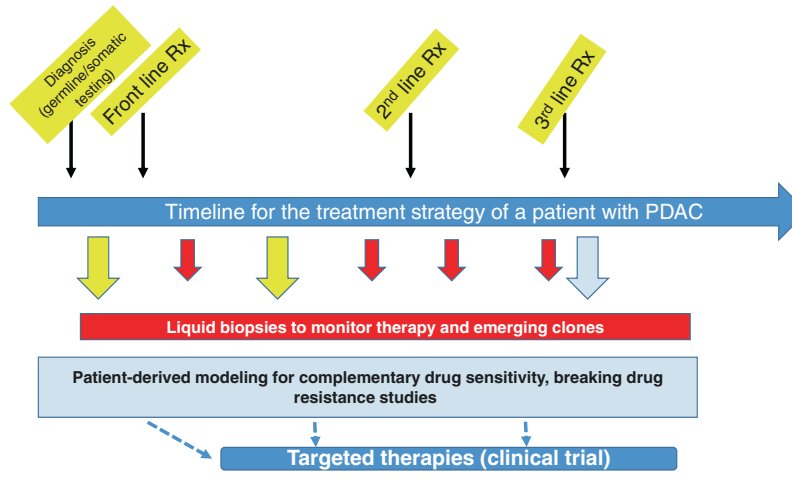

Fig. 21.2 The future vision of precision therapy strategy for the treatment of PDAC. Yellow highlight depicts where precision medicine is at currently

Concluding Remarks

We have entered an era where biomarker testing for cancer, to identify predictive markers of response to specific therapies has become the norm, and therapy for specific patient subgroups has become transformative, for example, for EGFR-mutated non-small cell lung cancer, MSI-High cancers, and cancers that harbor NTRK fusions. This is also now a reality in PDAC, and recognizing this, the NCCN has recommended molecular profiling for all advanced PDAC patients. As described above, we have demonstrated that PDAC patients who are profiled, and treated with appropriately matched therapies have a significantly improved survival as compared to similar patients who were not treated with matched therapy. Yet, one of the understandable criticisms is that PDAC patients do not have adequate access to matched therapy if molecular profiling reveals an actionable mutation.

For this reason, we and multiple other groups have been working to change the clinical trial landscape for PDAC patients, and to focus on biomarker-driven trials focused on small subgroups of patients. These trials are intended to demonstrate a high degree of activity, as demonstrated a clinically meaningful enhanced objective response rate; and/or a clinically meaningful prolongation of response. The best example to date in pancreatic cancer continues to be PARP inhibitor-based therapy for *BRCA1/2*-mutated PDAC, but even with a 20% ORR, and in the case of the POLO trial, a 7.3 month PFS, there is still significant room for improvement in outcomes. As another example of this, in a recent update on outcomes for MSI-high patients treated with pembrolizumab, Marabelle et al. did separate out the disease subgroups and, disappointingly despite all the hope of immune checkpoint inhibitors for MSI-High tumors, the PDAC patients only had a PFS of 2.1 months—both far less than other disease types [35].

Developing such biomarker trials one trial, and one target at a time is an inefficient, and more importantly slow process. Thus, we are working towards developing an umbrella protocol through which PDAC patients anywhere in the United States can undergo molecular screening, and then be directed to one of a series of biomarker-specific trials. This effort, called TARGET-Panc, is anticipated to launch in 2020, and parallels a similar effort in the UK known as Precision Panc. TARGET-Panc may also be a feeder into the US-based Precision Promise, which will sponsor a number of Phase III trials that, if successful, would lead to FDA approval/label indication for a biomarker-specific subgroup of PDAC patients. We are hopeful that within the next 3–5 years, we will see approval of several agents for biomarker-specific subgroups of PDAC patients.

Finally, as we ultimately hope not just to prolong survival for PDAC patients, but to increase the cure rate. Thus, applying what has been learned about biomarker-specific therapy in advanced metastatic patients can and will be applied to patients with localized disease. By applying this precision medicine approach to potentially resectable PDAC might lead to higher responses, and more R0 resections. And using this approach for adjuvant therapy we hope could ultimately improve the cure rate.

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The Prospects of Immunotherapy in Pancreatic Cancer

22

Haoqiang Ying and Wantong Yao

The development of pancreatic ductal adenocarcinoma (PDAC) is tightly intertwined with immune system. Studies from PDAC mouse models and human patients have established the critical role of inflammation during the tumor initiation and progression [1]. Such chronic inflammation within malignant lesions and in the surrounding normal exocrine tissues leads to the establishment of exuberant stroma tissue which occupies majority of the tumor mass. The inflammatory and fibrotic microenvironment not only support tumor cell growth/survival, but also facilitate the escape of tumor cells from immune surveillance. Although conventional immune checkpoint blockade therapies have failed to elicit therapeutic benefit in both mouse and human PDACs, multiple approaches have been successfully adopted in preclinical models to disrupt immune suppressive mechanisms and boost T cell activity, providing rationale to design effective immunotherapy combinations in human PDAC.

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The Formation of Immune-Suppressive Microenvironment

Among solid tumors, PDAC is an immunologically "cold" tumor, characterized by relatively sparse T cell infiltration. Moreover, the function of infiltrating T cells in PDAC is largely abolished by a dominant immune suppressive microenvironment, which leading to the failure of many immunotherapy trials. Here we will discuss the underlying mechanisms for the overt suppressive immune microenvironment in PDAC.

Tumor Cell-Intrinsic Factors

One of the major tumor cell-intrinsic factors that drive T-cell mediated anti-tumor immunity is neoantigen load. Indeed, tumor mutational burden is significantly correlated with the objective response rate to immune checkpoint blockade (ICB), such as PD-1 inhibition [2]. Immunologically "hot" tumors with robust CD8+ T cell infiltration usually exhibit high mutational burden (around 10 mutations per Mb in melanoma). In contrast, the mutational burden of most sporadic PDAC is estimated to be around 1 mutation per Mb, a threshold less likely to elicit strong anti-tumor T cell response [3, 4]. However, hypermutation (>10 mutations per Mb)

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_22

does occur in rare population of human PDAC (~1%) with DNA mismatch repair (MMR) defect due to genetic alteration or epigenetic silencing of MMR genes, such as MLH1 and MSH2 [5]. Accordingly, the MMR deficient tumors showed abundant T cell infiltration and improved responses to PD-1 blockade [6]. In addition to neoantigen amount, neoantigen quality is also a key determinant for anti-tumor immunity. Analysis of long-term survivors of pancreatic cancer discovered that neoantigen homology to infectious-disease-derived peptides is a surrogate for neoantigen immunogenicity and identified MUC16 as one of such high quality neoantigens correlated with better prognosis [7]. Notably, tumor clones with high quality neoantigen tend to be lost in metastatic lesions [7]. Accordingly, T cell infiltration is significantly lower in metastasis compared to primary tumors [8], implicating enhanced immune editing during pancreatic cancer metastasis.

Tumor cells also play instrumental roles in orchestrating a strong immune-suppressive microenvironment, largely through the expression of various cytokines and chemokines induced by oncogenic KRAS, the dominant driver of human PDAC. For example, the recruitment of myeloid cells, the major immune suppressive cells, into tumor microenvironment (TME) is mediated by various cytokines, including IL-6, IL-13, CCL2, G-CSF, M-CSF, and GM-CSF, that are produced by tumor cells [9–13]. Tumor cells also induce the infiltration of additional immunosuppressive cells, such as regulatory T (T_{reg}) cells and γδT cells, through the expression of TGF-β or other mechanisms yet to be identified [14, 15]. PDAC is a heterogeneous disease composed of various subclones due to genetic alterations or epigenetic regulations. Notably, tumor subclones that express high level CXCL1 can act dominantly to establish the overall immunosuppressive TME through the recruitment of myeloid cells, even though the CXCL1+ clones consist minor fraction of the bulk tumor [16], underscoring the role of tumor cell heterogeneity in defining the immune microenvironment.

Stroma Fibroblast

One defining feature of human PDAC is its desmoplastic stroma, which often comprises majority of the total tumor mass. The physical property of PDAC stroma is one of the contributing factors that suppress the anti-tumor immunity. The dense extracellular matrix (ECM) proteins, mostly composed of collagen, is largely deposited by cancer-associated fibroblasts (CAFs) and creates a physical barrier limiting T cell infiltration toward tumor cells [17, 18]. Another abundant component of ECM is hyaluronan, which is a linear glycosaminoglycan composed of repeating glucuronic acid and N-acetyl glucosamine disaccharide units [19, 20]. CAFs are likely one of the major sources for hyaluronan as it is predominantly found within the desmoplastic stroma regions in human PDAC tissues [19]. The accumulation of hyaluronan in TME dramatically increases the interstitial fluid pressure, leading to the collapse of tumor vasculature and may impede T cell infiltration [20, 21]. Indeed, T cells are mostly trapped in the stroma component of PDAC and rarely infiltrate into the juxtatumoral region [8, 22].

The major immunosuppressive function of CAFs is exerted through the recruitment of various inflammatory cells to inhibit anti-tumor immunity. Multiple CAFs subpopulations have been identified in human PDAC, including a myofibroblast (myCAF) population characterized with active collagen deposition which may function to restrict tumor growth, and an inflammatory fibroblast (iCAF) population characterized with high level of cytokine expression and exhibiting tumor-promoting capacity [23, 24]. Accordingly, digital deconvolution of bulk PDAC transcriptomic data has classified PDAC CAFs into two major subtypes, a "normal" subtype resembling myofibroblast or the mCAFs and a "activated" subtype characterized with inflammatory signatures, resembling the iCAFs [25]. Importantly, the activated stroma subtype is significantly correlated with poor patient prognosis [25], underscoring the importance of the immune-regulating function of CAFs during PDAC development.

Among the cytokines/chemokines highly expressed in CAFs, G-CSF and CXCL1 are well-known chemoattractant for immune suppressive myeloid cells, whereas IL-6 functions to promote the differentiation of myeloid cells into myeloid-derived suppressor cells (MDSCs) [16, 26, 27]. In addition to the direct effect on myeloid cells, CAFs can function to regulate myeloid cell function indirectly through stroma-derived Cxcl13 to recruit B cell sub-populations which in turn promote the immunosuppressive polarization of tumor associated macrophages (TAMs) [28–30]. CAFs also secrete thymic stromal lymphopoietin (TSLP) which induces myeloid dendritic cells (DCs) to attract and polarize Th2 CD4+ lymphocytes, another immunosuppressive cell type in the TME [31]. Work from genetically engineered mouse (GEM) models of PDAC also identified CAF-derived Cxcl12 functioning to limit T cell activation and blocking CXCL12 interaction with its receptor CXCR4 promote CD8+ T cell infiltration [17].

T Lymphocytes

T lymphocytes are the major cellular components of the adaptive immunity and $CD8^+$ cells are the key executioners of anti-tumor immunity. The amount of $CD8^+$ cells within PDACs are quite variable and their cytolytic activity does not always correlate with increased neoantigen load in the tumor [32]. However, the abundance of $CD8^+$ T-cell infiltration within tumor in combination with tumor mutational burden seems to be predictive of patient outcome [7]. As previously mentioned, majority of $CD8^+$ T cells are stuck within the tumor stroma and rarely infiltrate into tumor nest [8, 22]. The infiltration of $CD8^+$ T cells to the juxtatumoral region (within 20 mm of tumor epithelium) does significantly correlated with better patient survival [33]. It should be noted that most tumor-infiltrating $CD8^+$ T lymphocytes (TILs) are antigen experienced ($CD45RO^+CCR7^-$ or $CD45RO^+CCR7^+$) and exhibit elevated expression of checkpoint molecules, including 4-1BB, PD-1 and LAG-3 [34]. However, they do not show the downregulation of T-BET and induction of EOMES [34], indicating the TILs are not terminally exhausted although their function is largely blunted by a variety of surrounding immunosuppressive cells.

The major modulator for $CD8^+$ T cell function is $CD4^+$ lymphocyte. Depletion of $CD4^+$ T cells in a PDAC GEM model leads to activation of $CD8^+$ T cells and suppression of tumor development, indicating the dominant function of CD4+ T cells is to suppress anti-tumor immunity [35]. Among the multiple $CD4^+$ T cell subpopulations, T_h1 cells function to induce $CD8^+$ T cell activation through the production of IL-2 and IFN-γ [36, 37]. On the other hand, T_h2 cells secrete IL-4, IL-5, and IL-10 to suppress the function of $CD8^+$ T cells [31, 38]. Accordingly, the ratio between T_h1 and T_h2 cells is correlated with anti-tumor immunity in PDAC [31, 39, 40].

T_{reg} cell is another major $CD4^+$ T cell population that is enriched in human PDAC [34, 35, 41]. T_{reg} cells are generally believed to suppress innate and adaptive immunity, including natural killer (NK) cells, DCs and B cells [42–44]. While T_{reg} cells have been indicated to promote PDAC growth through their immunosuppressive functions [45, 46], recent study in PDAC GEM model showed that depletion of T_{reg} surprisingly enhanced tumor development [47]. This is likely achieved through the loss of tumor-restricting myofibroblast and recruitment of immunosuppressive myeloid cells, including MDSCs and TAMs, as well as the induction of T_h2-type response in the TME [47]. These findings put a cautionary note on the effort to target T_{reg} cells in PDAC.

In addition to T_h2 and T_{reg} cells, T_h17 cells are also recruited to PDAC TME to promote PDAC development [48]. Inhibition of IL-17, the major cytokine released by T_h17 cells, suppresses tumor progression in PDAC GEM models which is accompanied with decrease in MDSCs, implicating that T_h17 cells may promote tumor growth at least partially through the suppression of anti-tumor immunity [48]. It should be noted that IL-17 is also secreted by an unconventional population of T cells, γδT cells, which are also recruited to the TME by KRAS-driven tumor cells [14, 48]. Depletion of γδT cells also

suppresses PDAC development in GEM model, supporting the pro-tumor function of γδT cells [14]. The tumor-infiltrating γδT cells express high level of T cell exhaustion ligands, such as PD-L1 and Gelectin-9, and co-depletion of αβT cells reversed the tumor progression phenotype induced by γδT cell depletion, indicating that the pro-tumor function of γδT cell is largely due to the inhibition of $CD4^+$ and $CD8^+$ cells.

Recent studies in mouse and human PDAC further identified additional unconventional T cell populations, such as the $TCR\alpha\beta^+CD4^-CD8^-NK1.1^-$ innate αβ T cells (iαβT) in the TME [49]. These iαβT cells function to enable $CD4^+$ and $CD8^+$ T-cell activation through the CCR5-dependent immunogenic polarization of TAMs, and therefore may serve as target for co-stimulatory immunotherapies [49].

Myeloid Cells

The major component of immune infiltration in PDAC are myeloid cells, including TAMs, granulocytes, and inflammatory monocytes [50]. TAMs account for the majority of myeloid infiltration in PDAC TME. They are highly plastic and can be polarized between the pro-inflammatory and anti-inflammatory phase. TAMs are recruited to TME and polarized toward anti-inflammatory phase by various cytokines, such as M-CSF, CCL2, and BAG3 released by tumor cells to suppress anti-tumor immunity [51–53]. On the other hand, when polarized toward pro-inflammatory phase, TAMs can function as antigen-presenting cells to activate $CD8^+$ cells and secrete pro-inflammatory cytokines to suppress tumor growth [54, 55]. Another major immunosuppressive myeloid cell population is MDSC. They are recruited to TME at the early onset of PDAC development by a variety of cytokines/chemokines, including G-CSF, M-CSF, GM-CSF, IL-3, IL-6, and CCL2 [9, 12, 50, 56, 57]. These immunosuppressive myeloid cells mitigate anti-tumor immunity by direct inhibition of CD8+ T cells activity or induction of checkpoint ligand, such as PD-L1, in tumor cells [9, 12, 58, 59]. A minor fraction of tumor-infiltrating myeloid cells are the DCs. Fully activated DCs function as professional antigen-presenting cells to mediate anti-tumor immunity. However, circulating DCs and their progenitors are decreased in PDAC patients [60]. In addition, tumor cells also directly suppress DC maturation in the TME through the expression of various cytokines, such as IL-6 and G-CSF [60, 61]. In contrast to the perceived anti-tumor activity, accumulating evidence indicates that tumor-associated DCs actually promote PDAC growth by directly inhibiting $CD8^+$ T cell function through Arginase 1 (ARG1)-mediated arginine depletion in the TME or indirectly through the induction of Tregs with IL-23 and TGF-β, as well as the priming of naïve T cells toward Th2 polarization [39, 62–64].

Metabolism Environment

The PDAC TME is characterized by sustained and severe hypoxia and depletion of nutrients such as glucose and glutamine due to dense stroma [65, 66]. Such hostile microenvironment forces CD8+ T cells to rely on glycolysis with limited supply of glucose, leading to PD-1 mediated T cell exhaustion and dysfunction [67, 68]. Enhanced glycolysis is a defining feature of PDAC metabolism, which is further activated by the hypoxia microenvironment [69]. Such metabolism feature of PDAC results in the accumulation of lactate in PDAC TME, which promotes the anti-inflammatory polarization of myeloid cells, exacerbates $CD8^+$ T cell dysfunction, and inhibits NK cell activation [70–72]. Additionally, the immunosuppressive myeloid cells exhibit elevated expression of Arg1 [73]. This leads to the depletion of arginine in PDAC TME which is required for $CD8^+$ T cell activation [74]. Moreover, $CD8^+$ T cell function is further mitigated by the depletion of tryptophan, another key amino acid for its activation, in the TME, likely due to the overexpression of Indoleamine 2,3-dioxygenase (IDO) in tumor cells [75].

Microbiome

There is growing appreciation for the roles of the gut and intra-tumoral microbiome during the carcinogenesis of PDAC. Studies using PDAC GEM models have provided evidence for the potential translocation of gut bacteria to tumor site and demonstrated that gut dysbiosis is associated with the development of pancreatic tumor [76]. Importantly, these tumor-associated bacteria species are correlated with increased immunosuppressive myeloid cell infiltration and dampened $CD8^+$ T cell activation, therefore promoting tumor development [76]. In addition to bacteria, fungi species, in particular *Malassezia spp.*, are also identified in both human and mouse PDAC, which function to activate complement cascade and promote PDAC development through complement receptors on tumor cells [77]. These studies implicate the potential of antibiotic therapies to improve the anti-tumor immunity in PDAC. However, it should be noted that not all gut or intra-tumoral microbes are pro-tumor growth. It has been shown in human PDAC patients, that a unique intra-tumoral microbiome signature, including *Pseudoxanthomonas, Saccharopolyspora, and Streptomyces spp.*, is capable of inducing anti-tumor immunity and is associated with long-term survival [78].

The Current Status and Prospect of Immunotherapy

While immunotherapy has radically changed the therapeutic prospect of many cancer types, it has gained limited success for the treatment of PDAC. Multiple strategies are being tested to harness the anti-tumor immunity and there are currently over a hundred immunotherapy trials for PDAC ongoing in the USA. Here we will summarize some of the lessons and progress we have gained from multiple preclinical and clinical studies and discuss the prospect of immunotherapy strategies.

Immune Checkpoint Blockade

Leveraging T cell-mediated adaptive anti-tumor immunity has been the major theme of current immunotherapy and most of the success of treating solid tumor is based on ICB. However, PDAC is notoriously resistant to conventional ICB, such as anti-CTLA4 and anti-PD-L1 therapies [79, 80], with the exception of ~1% patients with increased neoantigen load due to MMR deficiency [6]. Total of eight PDAC patients were recruited in the anti-PD-1 trial and the objective response rate was 62% with three patients showing partial response and two patients showing complete response [6]. While the PD-1 blockade showed durable response in MMR deficient PDAC patients, a case of acquired resistance with localized ovary metastasis was reported [81]. However, continuous response to immunotherapy is sustained in the patient following local surgery treatment, underscoring the therapeutic benefit of ICB in MMR deficient patients. Beyond PD1/PD-L1 and CTLA4, additional immune checkpoints, including co-inhibitory molecules (LAG-3, TIM-3, and VISTA, etc.) and co-stimulatory molecules (4-1BB, OX40, CD27, and GITR, etc.) have been characterized and are evaluated as targets for PDAC immunotherapy [82–85]. It should be noted that ICB is unlikely to achieve meaningful response without correcting the overly suppressive immune microenvironment of human PDAC.

Tumor Vaccine

One approach to induce and active TILs is using vaccines. One of the most well-developed PDAC vaccines is GVAX, which is an allogenic whole-cell vaccine derived from two irradiated human PDAC cell lines engineered to release GM-CSF at the vaccination site [86]. Initial phase I trials of GVAX or GVAX in combination with low-dose cyclophosphamide to deplete T_{reg} in patients with advanced PDAC patients showed minimal treatment-related toxicity and evidence

of $CD8^+$ T cell activation, as well as induction of intratumoral tertiary lymphoid aggregates [87–89]. However, phase II study of 60 patients with resected PDAC failed to achieve significant improvement in overall survival compared to a historical cohort treated with surgery followed by adjuvant chemoradiation [90]. Nevertheless, mesothelin was identified as vaccine-induced $CD8^+$ T cell target associated with prolonged survival in GVAX -treated PDAC patients [90, 91], prompting the development of a live-attenuated Listeria monocytogenes-expressing mesothelin vaccine, CRS-207. While an initial phase I trial of CRS-207 as booster vaccine in combination with GVAX exhibited promising survival benefit compared to GVAX alone group, a subsequent, larger phase II trial failed to achieve improvement in overall survival in metastatic PDAC patients treated with GVAX and CRS-207 combination in comparison to chemotherapy group [92, 93]. Additional combinatory strategy combining GVAX with CTLA-4 antagonist was evaluated in a phase Ib trial in chemo-resistant PDAC, which showed a trend toward improved survival for patients receiving the GVAX/ipilimumab combination [94]. Subsequent T cell receptor (TCR) repertoire analyses from PDAC patients treated with GVAX in combination with CTLA-4 or PD-1 blockade indicated diversification of peripheral TCR repertoires, in particular in GVAX/ipilimumab-treated group, provides the rationale to evaluate additional combination strategies of GVAX and ICB. Additional strategy to boost the GVAX response was also tested, including the development of STINGVAX where the GVAX was co-formulated with STING agonist. STING functions in the intracellular DNA-sensing pathway to induce robust type I interferon and proinflammatory cytokine responses. Treatment of STINGVAX in combination with PD-1 blockade elicit strong $CD8^+$ T cell activation and induced regression of established tumors in preclinical models [95]. It should be noted that simply boost vaccine-induced T cell response is unlikely to yield meaningful clinical benefit. Intratumoral leukocyte analysis of GVAX-treated PDAC showed abundant myeloid infiltration correlated with T cell exhaustion phenotype [96], underscoring the need to co-target the immunosuppressive TME to improve the efficacy of tumor vaccine therapies.

Adoptive Cell Therapy (ACT)

ACT is a highly personalized cancer immunotherapy referring to the administration of tumor-reactive immune cells that have been selected and expanded ex vivo. ACT largely involves naturally occurring $CD8^+$ T cells with antitumor activity or genetically engineered cytotoxic T cells that recognize neoantigens unique for tumor cells or antigens highly overexpressed on tumor cells compared to normal tissues. The ubiquitous presence of oncogenic KRAS mutations makes them ideal candidates for ACT. However, KRAS mutations are generally considered non-immunogenic, probably due to limited processing or low affinity to HLA alleles [97]. Nevertheless, T cells recognizing $KRAS^{G12V}$ or $KRAS^{G12D}$, the most common KRAS mutations in human PDAC, have been identified to be associated with HLA-A*11:01 and HLA-C*08:02 alleles [98, 99], implicating the utility of KRAS-specific ACT in a small fraction of PDAC patients harboring these HLA alleles. T cell receptors recognizing PDAC neoantigens other than mutant KRAS have since been identified in patients [100], provide additional potential targets for ACT using native peripheral or tumor-infiltrating T cells.

However, high affinity T cells specific to tumor neoantigens are likely to be depleted during PDAC development. Genetic approaches, including cloned T cell receptors (TCR) or chimeric antigen receptors (CAR), have thus been adopted to engineer T cells that can recognize tumor antigens with high affinity. Mesothelin (MSLN) was identified as a tumor antigen that is overexpressed in majority of human PDAC [101]. Infusion of T cells engineered with MSLN-TCR into PDAC GEM model showed increased T cell infiltration in the tumor and enhanced anti-tumor immunity [101], providing rationale for further evaluation in clinical trials. In addition to TCR, MSLN-specific CAR has also been developed and a phase I trial in metastatic PDAC patients using

autologous T cells genetically modified with mRNA to transiently express the MSLN-CAR showed promising results with 2 out of 6 patients exhibiting stable disease without obvious toxicity, which is a serious concern for CAR-T therapy [102]. In addition to toxicity due to the expression of CAR-specific antigens in normal tissues, chronic TCR signaling-induced T cell exhaustion and the immune suppressive TME are also major factors limiting the efficacy of CAR-T therapy in solid tumors [67]. Multiple approaches have been taken to overcome such hurdle. Persistent T cell activation was observed in PDAC preclinical models treated with MSLN-CAR-Ts engineered with the intra-cellular domains (ICDs) of ICOS and 4-1BB [103]. In addition, a triple-engineered CAR-T has been developed which contains regular CAR specific for prostate stem cell antigen (PSCA), an antigen overexpressed in PDAC, and CARs recognizing immune suppressive cytokines, such as TGFβ or IL4, and are fused with the 41BB or IL7R endodomains, respectively [104]. Such design converts the signals from immunosuppressive cytokines, such as TGFβ and IL4, into T cell stimulation signaling, therefore sustaining T cell activation. The intra-tumoral heterogeneity may also undermine the impact the CAR-T cells. To bypass this, a biopolymer scaffold was designed to co-deliver CAR-T cells and STING agonists directly to pancreatic tumors in preclinical models which resulted in not only the elimination of tumor cells specifically recognized by CAR, but also the depletion of tumor cells without CAR-specific antigen due to the induction of anti-tumor immunity by STING agonist [105]. The efficacy of CAR-T therapy in PDAC and other solid tumors is likely to be greatly improved with the development of new generations of CAR-T cells.

CAR has also been adopted in additional immune cells other than T cells, such as NK cells to generate CAR-NK cells. As NK cells can be derived from allogenic sources, such as cord blood, and can be used in patients without the need for full HLA matching, CAR-NK cells can be used off-shelf, instead of the highly personalized design of CAR-T cells, which gives CAR-NK cells unique advantage over conventional CAR-T therapies. While anti-CD19 CAR-NK therapy showed strong anti-tumor effect in CD19+ hemopoietic cancers, its effect in solid tumors, such as PDAC, remains to be further explored.

Targeting TME

One of the major reasons for the lack of the benefit from immunotherapy in PDAC is the immune suppressive microenvironment. While the dense stroma may impede the T cell infiltration, it also forms a barrier surrounding tumor cells. Simply depleting the stroma surrounding tumor cells with hedgehog inhibitor has been shown to promote tumor growth in both preclinical models and PDAC patients, leading to the halt of the clinical trial of hedgehog inhibitors. Alternative approaches have been developed to "normalize" the PDAC-associated stroma, including Vitamin D agonist and LIF inhibitor, which can slow down tumor growth and sensitize tumors to chemotherapy in preclinical models [106, 107]. Additionally, PEGPH20, a pegylated hyaluronidase, has been shown to decrease the hydrostatic pressure in the dense PDAC stroma and promote chemo-sensitivity due to improved drug delivery [20]. However, clinical trials of these agents in PDAC patients did not seem to recapitulate the improvement in chemo-sensitivity observed in preclinical models. Nevertheless, decreasing the hydrostatic pressure with PEGPH20 or targeting CAFs with FAK inhibitor seems to promote T cell infiltration and sensitize tumors to immunotherapies such as GVAX or ICB in preclinical models [21, 108], prompting additional trials of targeting tumor stroma in combination with immunotherapies.

As the major immunosuppressive component of PDAC TME, myeloid cells have recently emerged as prime immunotherapy targets to enhance anti-tumor immunity. Activation of CD40 on myeloid cells with an agonist antibody showed transient anti-tumor effect in PDAC GEM models through the reprogramming of TAMs toward pro-inflammatory phase

and priming the T cells with additional chemotherapy, such as gemcitabine or nab-paclitaxel, leads to sustained anti-tumor effect [109–111]. Similar combination has showed promising therapeutic effect in a phase 1b trial [112], raising the hope to achieve sustainable immunotherapy response in PDAC patients. Activation of CD11b, a cell surface marker of myeloid cells, with small agonist also induced the pro-inflammatory polarization of TAMs, enhanced DC responses and sensitized PDACs to ICB [113]. Targeting additional cytokine receptors on myeloid cell surface, including CXCR2, CCR2, and CSF1R, or myeloid-specific signaling molecules required for their anti-inflammatory polarization, such as PI3Kγ, has been shown to deplete myeloid cells, improve anti-tumor immunity, and reduce tumor burden [53, 114–116]. More recently, additional checkpoint molecule, such as VISTA, has been found to be overexpressed on TAM surface and block TIL activation, indicating the need to target such alternative checkpoint to achieve full activation of anti-tumor immunity [8].

Since the remodeling of TME, including the CAFs and recruitment of immunosuppressive immune cells, is largely orchestrated by oncogenic signaling in tumor cells, successful targeted therapy is expected to not only deplete tumor cells through cell-autonomous manner, but also activate anti-tumor immunity to eliminate tumor cells. Indeed, treatment of AMG510, a small molecule inhibitor for $KRAS^{G12C}$, which is presented in ~1% human PDAC, promoted the infiltration of pro-inflammatory TAMs, enhanced $CD8^+$ T cell infiltration/activation and synergized with immune checkpoint blockade to induce complete tumor regression in preclinical models [117].

Conclusion

An effective therapeutic strategy to achieve sustainable antitumor immunity should be composed of at least three key components: (1) a proper method, e.g. irradiation, chemotherapy, or effective targeted therapy, that destroys tumor cells and release large amount of tumor antigens to prime the immune system; (2) recruitment and activation of effector T cells; and (3) reverse the immune suppressive environment to sustain the anti-tumor immunity. This will require a combination of approaches to target various components of the tumor ecosystem, including tumor cells, stroma cells and immune compartment, probably in a sequential manner. It is possible to achieve curable outcome for PDAC patients with the development of effective targeted therapy and combinatory immunotherapies.

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Microbiome in Pancreatic Cancer

23

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Introduction on Microbiome

The highly complex, vast reservoir of commensal micro-organisms comprising of bacteria, fungi, and viruses that reside in various locations within our bodies is known as the microbiome [1]. Microbiota and microbiome are two terms often used interchangeably but they denote distinct meanings [2]. Microbiome refers to the entire habitat encompassing all the microbes and their genomes while microbiota is used to describe the composition of microbes residing in a specific environment [2]. Metagenomics refers to the collection of genes and genomes within a specific environment that can also be used to understand their functional profiles [2]. The microbiome is an important player affecting host physiology through interactions with host cells to alter host metabolism and immunity. The largest community of such microbes reside in the gastrointestinal tract and is known as the gut microbiome while other prominent hot-spots can be found in the oral cavity and the skin.

Early investigations of the microbiome were limited to culture-based technologies which lead to detection and further study of only select microbial species. With the advances in sequencing methodologies comprising of shotgun metagenomic sequencing as well as 16S ribosomal RNA (rRNA) gene sequencing and analysis, detailed microbial sequences have been reported of healthy individuals through the Human Microbiome Project [1]. Shotgun metagenomic sequencing involves sequencing all the genomic material in the sample, mapping it to a reference genomic database which provides detailed information about both the host as well as foreign microbial sequences, affording a comprehensive and detailed composition of the sample which can be used to infer microbial functional profiles as well [3]. Shotgun metagenomic sequencing is viewed as a more reliable approach for confidently predicting microbial species but may not always be desirable. Since it involves sequencing all of the genomic content in the sample, it incorporates both microbial and non-microbial (host) reads which can obscure results, especially during human microbiome studies using low microbial biomass sample types such as tumors. Additionally, it is quite expensive making it an unattractive choice if numerous samples need to be processed across

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_23

multiple time-points. A more streamlined approach is the use of 16S rRNA gene sequencing which relies on amplifying the ribosomal sub-unit of the prokaryotic 16S gene, conserved among all bacteria [4]. Further discrimination of different bacterial species is achieved by sequencing a sub-set of nine hypervariable regions (V1-V9) of the 16S rRNA gene which are sufficiently variable between different species to allow for identification and phylogenetic discrimination [4]. The 16S variable region 4 (16S V4) rRNA is approximately 254 base-pairs long and its paired end reads allows for almost complete overlap to generate reliable data for performing microbial phylogenetic analyses without the need for sequencing the entire gene. 16S V4 rRNA gene sequencing is also viewed as a relatively inexpensive methodology for microbial detection of both high and low bio-mass sample types.

Since the improvement of the detection capabilities, the microbiome is increasingly recognized for its integral role in influencing disease outcomes. Consequently, the microbial signatures associated with various diseases have been widely reported ranging from obesity, cancer, autoimmune, inflammatory, and neurological conditions. Early reports of the microbiome had been mostly descriptive and limited to primarily describing the gut microbial signatures as obtained from analyzing fecal samples of various cancer types. The microbial alpha-diversity is a commonly used measurement to indicate the number of species that is present within a sample [1]. Patients with colorectal, breast, and pancreatic cancer had been found to have lower alpha diversity than healthy controls [5–7]. Patients with melanoma who responded to immunotherapy were found to have higher alpha diversity compared to non-responders [8].

Microbial Biomarkers in Pancreatic Cancer

Several clinical studies have examined the relationship between the microbiome and pancreatic cancer risk and occurrence. Microbiome samples, especially those that can be obtained non-invasively such as oral and fecal samples, have emerged as a novel reservoir for identifying early biomarkers for disease risk prediction.

Periodontal disease was first associated with an elevated risk for pancreatic cancer [9] and was postulated as an initiator of oral dysbiosis. Analysis of the oral microbiome found an association between two oral bacteria *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* and increased risk for pancreatic cancer [10]. Plasma antibodies against one of these bacteria, *Porphyromonas gingivalis*, were reported to correlate with reduced risk of pancreatic cancer [11], suggestive of systemic immunity gained by pancreatic cancer associated oral pathogens. In another study on oral microbiome, the following two bacteria were highly useful to distinguish pancreatic cancer patients from healthy controls—*Neisseria elongata* and *Streptococcus mitis* [12].

The gut microbiome associated with pancreatic cancer has been described in various clinical studies. A study performed in China evaluated the gut microbial profiles in a cohort of patients with pancreatic cancer and matched healthy controls. A microbial signature unique to pancreatic ductal adenocarcinoma (PDAC) patients was detected, which included enrichment for *Veillonella*, *Klebsiella*, *Selenomonas* genera, and LPS-producing bacteria (*Prevotella*, *Hallella*, and *Enterobacter*) while *Bifidobacterium* genus and some butyrate-producing bacteria (*Coprococcus*, *Clostridium IV*, *Blautia*, *Flavonifractor*, and *Anaerostipes*) were decreased [7]. However, when the patients presented with complications like biliary obstruction, their gut microbial signatures diverged from other PDAC patients [7]. These differences could be attributed to possible metabolic perturbations downstream of biliary fluid stasis. Another study which examined gut microbial signatures of pancreatic cancer patients vs. healthy controls, in two independent cohorts from China and Israel, reported an increase in *Bacteroidetes* and a reduction in *Firmicutes* in pancreatic cancer patients [13]. An additional study reported enrichment of *Proteobacteria*, *Synergistetes*, and *Euryarchaeota* in the gut microbiome of PDAC patients when compared to matched healthy controls [14]. Nonetheless, it has been challenging to discern a

globally unifying microbial group as a perpetrator of disease primarily due to wide scale differences in geography and lifestyle preferences. It is, therefore, highly imperative that functional profiles of disease-associated microbiomes are understood so that downstream dysbiotic mechanisms could be directly targeted.

Mounting evidence is indicating that the gut microbiome may not be the only important player in influencing tumors. Intratumoral bacteria has been implicated as an important component of the tumor microenvironment that can influence tumors growth and responses to therapies [15, 16]. Studies focused on characterizing the microbial composition of matched gut and tumor clinical samples suggest a gut-to-tumor microbial cross-talk that promotes translocation of microbes from the gastrointestinal tract into the pancreatic tumors [16], which may occur through the biliary duct, by reflux from the duodenum or via the bloodstream.

Even pancreatic premalignant cystic lesions have been reported to harbor abundant bacteria [17, 18]. Cystic lesions of numerous types such as intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCN), serous cystadenomas (SCA), pseudocysts, and others have been found to contain bacteria with enrichment of *Bacteroides*, *Escherichia/Shigella*, *Fusobacterium*, *Acidaminococcus*, *Sphingomonas,* and *Bifidobacterium* [18]. Others have reported that higher-grade IPMNs are enriched with common oral pathogens such as *Fusobacterium nucleatum* and *Granulicatella adiacens*, but allude to their translocation from oral cavities to the pancreatic cysts partially as a result of invasive endoscopic procedures [17]. The presence of bacteria inside pancreatic tumors was first reported in 2017 and specifically the class Gammaproteobacteria was enriched in PDAC tissues [15]. This class of bacteria produces the enzyme cytidine deaminase which can inactivate the chemotherapeutic drug gemcitabine, backbone of one of the two most common chemotherapy regimens used for pancreatic cancer treatment [15]. A more recent comprehensive study has defined the presence of bacteria across different solid tumor types including melanoma, breast, lung, ovary, bone, and brain cancers as well [19]. This study was unique as it used several methodologies including multiplexed sequencing of the five regions covering different conserved and hypervariable regions of the 16S rRNA gene (5R 16S rRNA) which allowed for higher coverage and more accurate predictions from low quality formalin-fixed paraffin embedded (FFPE) tumor samples, along with immunohistochemical staining for 16S rRNA through fluorescence *in situ* hybridization (FISH) and bacterial proteins like lipopolysaccharide (LPS) and lipoteichoic acid (LTA) to visualize Gram-positive and Gram-negative bacteria, respectively [19]. Besides the direct characterization of tumor microbes by 16S rRNA sequencing, novel computational pipelines have been developed to extract non-human microbial sequences from tumors and blood sequencing datasets from The Cancer Genome Atlas (TCGA). These methodologies enable identification of microbial signatures of healthy vs. cancer, and can discriminate between tumor types based on the tumor–microbes using artificial intelligence algorithms [20].

In a separate study from Riquelme et al., the PDAC tumor microbiome of two different cohorts of PDAC patients was defined [16]. Although overall tumor microbiome composition was similar to previously reported studies, primarily in the abundance of Gammaproteobacteria, patients with the most favorable prognosis (≥5 years overall survival, long-term survivors) had a higher intratumoral alpha-diversity compared to patients with <5 years survival (short-term survivors). A unique microbial signature containing *Pseudoxanthomonas*, *Streptomyces*, *Saccharopolyspora*, and *Bacillus clausii* was associated with long-term survivors, and correlated with tumor immune infiltration of cytotoxic T cells. Using PICRUSt analysis—a method that allows prediction of functional pathways based on 16S rRNA sequencing data, reference genomes, and metabolic reconstruction through KEGG analysis, distinct metabolic pathways were found differentially enriched in long- and short-term survivors. Nonetheless, the direct or indirect effects induced by microbial-associated

metabolites still remain to be fully explored and validated.

Modulation of the gut microbiome can be achieved through various strategies. One of them involves ablation of dysbiotic microbiomes through the use of antibiotics [14, 21, 22] but this approach will lead to non-specific depletion of broad classes of microbes and their over-use could likely promote antibiotic resistance [23]. Another strategy involves the use of fecal microbiota transplantation (FMT) wherein whole communities of gut microbiota are transferred to a patient either through a colonoscopic procedure or non-invasively in the form of oral pills which encapsulate frozen or lyophilized fecal material [24]. Recently in early phase I clinical trials for immunotherapy refractory melanoma patients have been shown to be successfully converted into responders after fecal transplantation from donors who had previously responded to anti-PD-1 (Programmed cell death protein 1) based immunotherapy [25, 26]. Autologous FMT has been used for reconstitution of baseline gut microbial profile in cancer patients receiving radiation therapy or irradiation for bone-marrow transplantation as well, as it can drastically reduce the severity of intestinal inflammation and improves outcomes [27]. FMT from healthy donors is also being used to reduce immune checkpoint inhibition related cytotoxicity in cancer patients in ongoing clinical trials [28] (Table 23.1).

Role of Pancreatic Microbiome in Preclinical Studies: Exploring Functional Relevance

Preclinical animal models have been instrumental in improving our understanding of how the microbiome can impact pancreatic tumor growth and responses through modulation of the immune and metabolic systems. The gut microbiome of a transgenic PDAC mouse model- KC (Ptf1aCre; LSL-$Kras^{G12D}$) was found to be enriched with *Actinobacteria* and *Bifidobacterium pseudolongum*, which progressively increased with age and disease progression [14]. Ablation of commensal microbes either through the development of KC mice re-derived in a germ-free environment or through the use of antibiotics in wild-type (WT) mice bearing orthotopic tumors resulted in significantly reduced tumor growth [14]. The tumor-promoting role of the microbiome was further confirmed when FMT from an aggressive PDAC mouse model- KPC (LSL-$Kras^{G12D}$, LSL-$Trp53^{R172H}$, Ptf1aCre) drastically accelerated tumor growth in WT recipients bearing orthotopic tumors [14]. Immunosuppressive monocytic cells such as myeloid-derived suppressor cells (MDSCs) and macrophages expressing activated toll-like receptors (TLRs) were activated downstream of the protumorigenic dysbiotic microbiome which concurrently lead to deactivation of type I lineage CD4 and CD8 T cells, altogether leading to the development of an immunosuppressive tumor microenvironment (TME) [14]. This immunosuppressive landscape of the TME could be reversed with the use of systemic antibiotics in WT mice bearing orthotopic tumors and further reconstituted with FMT from KPC mice [14].

To ascertain the ability of the microbiome to alter the metabolic system and affect tumor growth, gut microbial profiles of PDAC animal models have been examined. Metagenomics have been used to predict metabolic pathways to monitor changes in the gut microbiome with disease progression [29]. Using the KPC mouse model, it was found that metabolic pathways involved in biosynthesis of pyrimidines and polyamines, in particular those involving putrescine, spermidine, and spermine were significantly increased with PDAC development [29]. Higher serum levels of polyamines was detected in KPC mice with advanced stages of diseases, as well as in clinical serum samples from PDAC patients [29]. In subcutaneous KPC mice models, similar benefit of antibiotic use has been documented with reduced tumor growth through decrease in interleukin 17A (IL-17A) and interleukin 10 (IL-10) producing T cells while increasing interferon-gamma producing cytotoxic T cells [22]. In other transgenic models of PDAC ($Kras^{G12D/+}$, $PTEN^{lox/+}$, Pdx1-Cre), ablation of the microbiome with the use of antibiotics also reduced tumor growth [30].

Intratumoral pancreatic microbiome has been thoroughly studied in animal models as well. To generate a clinically relevant microbial preclinical model, one study treated WT mice with FMT from human donors to establish a baseline microbial composition representative of the patient population, followed by orthotopic transplantation with syngeneic KPC tumor cells [16]. Initial observations from this mouse model demonstrated that orally administered FMT microbes expectedly colonized the gastrointestinal tracts of the recipient mice but a notable amount colonized the murine tumors as well [16]. To tease apart the differential effects of the donor microbiome on recipient murine tumor growth, three types of donors were employed—healthy controls (HC), long-term survivors of PDAC with no evidence of disease at time of fecal specimen collection (LTS-NED), and PDAC patients with active disease or short-term survivors (STS). Orthotopic KPC tumor bearing mice receiving LTS-NED FMT had the smallest tumor sizes, lowest levels of TME immunosuppressive cells such as MDSCs and regulatory T cells, and highest levels of cytotoxic CD8 T cells expressing granzyme B and interferon-gamma [16]. On the other hand, mice receiving STS FMT had the largest tumor sizes and higher levels of immunosuppressive cells, while the HC FMT group had intermediate tumor sizes and minor reduction in TME immunosuppression [16]. The beneficial effect of the LTS-NED FMT was lost with concurrent use of antibiotics or the depletion of cytotoxic CD8 T cells with the use of neutralizing antibodies [16]. All of these preclinical studies have been instrumental is reinforcing the relevance of the microbiome in functionally affecting pancreatic cancer biology and clinical outcomes (Fig. 23.1).

Ongoing Clinical Trials for Targeting the Microbiome During Cancer

FMT was initially employed as a treatment strategy for microbial infections such as recurrent *Clostridium difficile* infection (CDI). Currently there are several ongoing clinical trials investigating the effectiveness of FMT in treating autoimmune and inflammatory conditions like ulcerative colitis (UC) and inflammatory bowel disease (IBD), gastrointestinal symptoms associated with neurological conditions like Parkinson's disease and autism spectrum disorder (ASD) in addition to multiple-drug resistant infections. For cancer clinical trials, FMT has been explored as a single agent or in combination therapy to reduce cytotoxicity associated with chemotherapy and immunotherapy (Table 23.1).

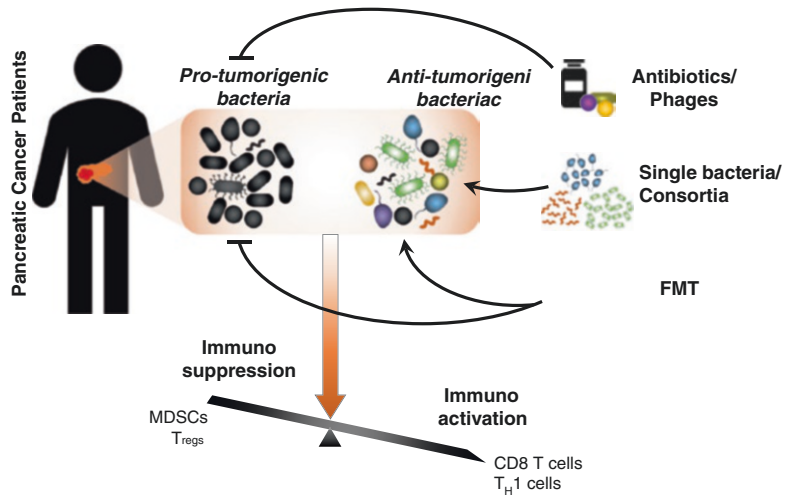

Fig. 23.1 Schematic diagram showing different approaches to microbiota modulation for cancer treatment. The overall goal is to shift the TME from an immunosuppressive to an immune-activated state. FMT, fecal microbiota transplantation; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; T_H1, type I helper

Image has already been published. http://dx.doi.org/10.1136/gutjnl-2019-319807

Table 23.1 Summary of ongoing clinical trials involved microbial-based approaches for cancer patients, reported in ClinicalTrials.gov as of January 2021

NCT no.	Cancer type	Therapy	Mode of FMT delivery
NCT04130763	GI cancers	Anti-PD-1	Capsules
NCT03353402	Melanoma	Refractory to immunotherapy	Colonoscopy & Capsules
NCT03838601	Head & Neck Squamous Cell Carcinoma	Chemoradiotherapy	Colonoscopy
NCT03686202	All solid tumors	PD-1/PD-L1 inhibitors	Capsules
NCT04040712	Renal cell carcinoma (RCC)	Tyrosine kinase inhibitors (TKIs)	Colonoscopy
NCT03819296	Melanoma, GU cancers	Prednisone, infliximab, vedolizumab	Colonoscopy
NCT04163289	Renal cell carcinoma (RCC)	Anti-PD-1, anti-CTLA-4	Capsules
NCT03341143	Melanoma	Anti-PD-1	Endoscopy
NCT02928523	Acute myeloid leukemia (AML)	Chemotherapy, antibiotics	Colonoscopy
NCT04056026	Mesothelioma	Anti-PD-1	Colonoscopy
NCT04116775	Prostate cancer	Anti-PD-1, Enzalutamide	Colonoscopy
NCT03772899	Melanoma	Anti-PD-1, anti-CTLA-4	Capsules

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Early Drug Development in Pancreatic Cancer

24

Shubham Pant and Rishi Surana

Introduction

Advancements in multimodal chemotherapy regimens over the past 10 years have improved survival rates for patients with metastatic pancreatic cancer. Despite these advancements, the overall survival of patients with metastatic pancreatic cancer remains dismal and there is an urgent need for more effective treatments to improve both the quantity and quality of life of patients with advanced pancreatic cancer. Phase I studies are a critical mechanism to arbitrate the safety (and in the case of phase I/II studies, an early glimpse of activity) of novel drugs and drug combinations. Malignancies such as pancreatic cancer which have a dearth of agents with proven therapeutic benefit are dependent on phase I trials to provide a pipeline of novel treatments. This chapter will focus on the general landscape of ongoing phase I trials in pancreatic cancer, with a particular focus on modulating tumor cell extrinsic (e.g., tumor microenvironment) factors and tumor cell-intrinsic vulnerabilities.

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Targeting the Tumor Microenvironment

T-Cell Checkpoint Inhibitors

As described in previous chapters, monotherapy with T-cell checkpoint inhibitors have largely failed to show clinical benefit in pancreatic cancer. The immune infiltrate of pancreatic cancer is predominantly composed of immunosuppressive myeloid cells (e.g., MDSC, M2 polarized macrophages) and T-regulatory cells (Treg), with a relative lack of functional effector T-cells; this immune suppressive microenvironment is hypothesized to be one of the main barriers to effective immune-based therapies in pancreatic cancer. There are several ongoing phase I trials combining checkpoint inhibitors with either chemotherapy, radiation or other targeted therapies in an attempt to try and overcome the immunosuppressive tumor microenvironment (Table 24.1). Combination therapy of anti-CTLA-4 and anti-PD-1 antibodies has demonstrated modest activity in pre-clinical models of pancreatic cancer and early attempts to utilize this combination therapy in metastatic pancreatic cancer have failed to show meaningful clinical

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_24

Table 24.1 Selected phase I/II clinical trials in pancreatic cancer

		Disease	Trial type	Primary outcome
Tumor cell intrinsic targets				
NCT01506973	Hydroxychloroquine + nab-paclitaxel	Locally advanced, metastatic	Phase I/II	OS
NCT01188785	siG12D LODER (local drug EluateR)	Locally advanced	Phase I	AE
NCT04132505	Binimetinib + hydroxychloroquine in KRAS mutant pancreatic cancer	Metastatic	Phase I	MTD
NCT03825289	Trametinib + hydroxychloroquine	Locally advanced, metastatic	Phase I	AE
Microenvironment targets				
NCT01485744	LDE225 + FOLFIRINOX	Locally advanced, metastatic	Phase Ib	MTD, toxicity
NCT03435289	Gemcitabine + nab-paclitaxel + CPI-613	Locally advanced, metastatic	Phase I	MTD
NCT03519308	Gemcitabine + nab-paclitaxel ± Paricalcitol	Resectable	Phase I	Safety
NCT03086369	Gemcitabine + nab-paclitaxel ± Olaratumab	Metastatic	Phase I/II	Safety, OS
NCT02210559	Neoadjuvant gemcitabine + nab-paclitaxel ± FG-3019	Locally advanced	Phase I/II	Safety, resection rates
Immunotherapy				
NCT02077881	Study of IDO inhibitor + gemcitabine + nab-paclitaxel	Locally advanced, metastatic	Phase I/II	MTD
NCT00836407	Ipilimumab ± vaccine therapy	Locally advanced, metastatic	Phase Ib	Tolerability, safety
NCT02526017	Cabiralizumab + Nivolumab	Locally advanced, metastatic	Phase I	Safety
NCT02305186	Capecitabine + RT ± Pembrolizumab	Resectable, borderline-Resectable	Phase I/II	DLT, TIL characterization
NCT04247165	Nivolumab + Ipilimumab + Chemoradiation	Locally advanced, metastatic	Phase I/II	Safety
NCT04161755	Tumor vaccine + Atezolizumab + FOLFIRINOX	Resectable	Phase I	Safety
NCT03086642	Intratumoral Talimogene Laherparepvec	Locally advanced, metastatic	Phase I	MTD
NCT02705196	LOAd703 + gemcitabine + nab-paclitaxel ± Atezolizumab	Locally advanced, metastatic	Phase I/II	DLT
NCT03281382	Intratumoral IL-12 transduced oncolytic virus + chemotherapy	Metastatic	Phase I	Safety
NCT03192462	TAA specific cytotoxic T lymphocytes	Resectable, locally advanced or metastatic	Phase I/II	Tolerability, safety

MTD Mean tolerated dose, *DLT* Dose limiting toxicity, *TIL* Tumor infiltrating lymphocytes, *OS* Overall survival, *AE* Adverse events

activity [1]. The anti-PD-1 antibody durvalumab was combined with the anti-CTLA-4 antibody tremelimumab in patients with metastatic pancreatic cancer but failed to meet pre-specified efficacy criteria [2]. Patients with refractory metastatic disease likely have rapidly progressive disease with deteriorating performance status and may not have a sufficient duration of treatment to receive a clinical benefit with checkpoint inhibitors. Thus, more recent phase I and phase I/II studies have utilized checkpoint inhibitor therapy in patients with localized disease (e.g., resectable, borderline-resectable or locally advanced disease). The LAPTOP trial is a phase I/II study is investigating the safety and activity of nivolumab and ipilimumab combined with radiation therapy in patients with locally advanced pancreatic cancer (NCT04247165). The rational for this study is based on the hypothesis that radiation therapy may augment the activity of immunotherapy by the so called abscopal effect, which hypothesizes that radiation therapy may prime the anti-tumor immune response, in part by releasing neoantigens and creating a pro-inflammatory milieu, that can lead to tumor responses outside of the radiation field [3].

Checkpoint inhibitors combined with chemotherapy is another active area of early phase clinical trials. Preliminary results from the phase I study of nivolumab combined with gemcitabine and nab-paclitaxel in patients with locally advanced or metastatic pancreatic cancer showed that this regimen is feasible to administer in this population with expected toxicities such as anemia and thrombocytopenia, hepatotoxicity [4]. Similarly, another phase I/II study examined the efficacy of the anti-PD-1 antibody pembrolizumab combined with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer [5]. Of the 11 chemotherapy naïve patients, 3 experienced a partial response (PR) and 8 experienced stable disease (SD). The incidence of immune related adverse events (irAE) was approximately 47% [5].

Combining checkpoint inhibitors with therapies aimed at overcoming microenvironmental barriers to generation of effective anti-tumor immune responses is a rational approach to boost the clinical efficacy of checkpoint inhibitors. CCL2 is abundant in the pancreatic tumor microenvironment and facilitates tumor infiltration of CCR2+ tumor-promoting macrophages. Inhibition of the CCL2/CCR2 axis enhances anti-tumor immune responses and decreased growth of pancreatic cancer in preclinical models [6]. Similarly, CCL5 can serve as a chemoattractant for myeloid cells but also recruits Treg to the pancreatic tumor microenvironment. These preclinical studies in part served the basis of the ongoing phase I/II study evaluating the safety and efficacy of BMS-813160 (anti-CCL2/CCL5) in combination with nivolumab, gemcitabine, and nab-paclitaxel in patients with borderline resectable and locally advanced pancreatic cancer (NCT03496662).

Vitamin D analogues have been demonstrated to increase T-cell infiltration and enhance drug delivery into the tumor microenvironment by modulating the activity of pancreatic stellate cells, which are critical sources of pro-tumor soluble mediators [7]. The vitamin D receptor agonist paricalcitol is being evaluated in phase II trials in combination with chemotherapy for patients with metastatic pancreatic cancer (NCT03331562). An ongoing phase I study is evaluating the safety of paricalcitol and pembrolizumab with or without chemotherapy in patients with resectable disease (NCT02930902).

Other Immune Based Strategies

Historically, vaccine-based approaches have held promise as a means to simultaneously overcome immune suppression in the microenvironment and elicit productive anti-tumor immune responses. Unfortunately, studies utilizing GVAX, a GMCSF-secreting allogeneic pancreatic tumor cell vaccine, as well as CRS-207, a live attenuated mesothelin expressing listeria monocytogenes, have demonstrated limited clinical activity. Talimogene laherparepvec (T-Vec) is a first in class oncolytic virus composed of a modified herpes simplex virus, type I (HSV-1) that co-ops aberrant type I interferon and protein kinase R signaling in tumor cells resulting in relatively tumor cell-selective replication and killing [8]. T-Vec is administered intra-tumorally and

is approved for use in patients with unresectable, recurrent melanoma and is currently being evaluated in a phase I trial in patients with refractory locally advanced or metastatic pancreatic cancer (NCT03086642).

Adoptive cellular therapies are actively being investigated in early phase trials in pancreatic cancer. Chimeric antigen receptor T-cells (CAR-T) are approved for relapsed refractory acute lymphoblastic leukemia and diffuse large B-cell lymphoma, but clinically significant efficacy in solid tumors has yet to be realized. A mesothelin-expressing CAR-T (CARTmeso) demonstrated safety in a phase I study of patients with pancreatic cancer that have progressed on two lines of chemotherapy. The best response was seen in two patients who had stable disease and had a progression free survival of 3.8 and 5.4 months [9]. Identification of an appropriate target antigen for CAR-T therapy is an important barrier to development of effective CAR-T therapy for pancreatic cancer and other solid tumors. Alternatively, adoptive T-cell therapy utilizing autologous T-cells primed with tumor associated antigens (NY-ESO-1, MAGEA4, PRAME, Survivin, and SSX2) are ongoing with interim analyses suggesting safety and efficacy (NCT03192462). A first in human autologous dendritic cell vaccine loaded with pancreatic tumor lysate is currently being evaluated in the adjuvant setting in an ongoing phase I study (NCT04157127).

Targeting the Stroma

The vast majority of the pancreatic tumor microenvironment is composed of stromal cells, of which cancer associate fibroblasts (CAFs) play a critical role in driving tumor growth, invasion, and chemoresistance. CAFs drive tumor growth in a multitude of ways, including secretion of soluble mediators such as SDF1, FGF1, VEGFA, which serve to drive tumor growth and angiogenesis. CAFs also express high level of TGF-B, PD-L1, PD-L2, and FasL all of which can serve to limit the generation of productive anti-tumor immunity. Alpha smooth muscle actin (aSMA) positive CAFs are critically dependent on signaling through the Hedgehog pathway and pancreatic cancer cells also utilize Hedgehog signaling for growth and survival. Preclinical data demonstrated that the smoothened inhibitor IPI-269609, which inhibits Hedgehog signaling, resulted in increased vascular permeability, increased intratumoral delivery of gemcitabine, and stabilization of disease in a mouse model of pancreatic cancer [10]. Unfortunately, a phase II study of vismodegib, a Hedgehog antagonist, in combination with gemcitabine failed to show clinical efficacy or improved drug delivery in patients with advanced pancreatic cancer [11]. There are ongoing studies evaluating Hedgehog signaling inhibitors in combination with chemotherapy and immunotherapy. A phase I study utilizing saridegib (Smoothened inhibitor) in combination with FOLFIRINOX is ongoing, with interim analysis suggesting that combination therapy is well tolerated (NCT01383538). Another ongoing phase I trial utilizing sonidegib (Smoothened inhibitor) in combination with FOLFIRINOX is currently ongoing (NCT01485744).

The novel peptide internalized-RGD (iRGD) is under developed and is hypothesized to increase intra-tumoral drug delivery in pancreatic cancer. iRGD, also named CEND-1, functions by binding to tumor specific integrins, leading to cleavage of the peptide which subsequently binds to neurolipin-1, and activates a novel pathway to facilitate drug delivery. Preclinical data demonstrated that iRGD improved intratumoral delivery of gemcitabine and the safety of this peptide is being evaluated in a phase I trial in combination with gemcitabine and nab-paclitaxel in patients with advanced pancreatic cancer [12] (NCT03517176).

Targeting Tumor Cells

KRAS-Based Targets

Point mutations in KRAS occur in approximately 90% of pancreatic adenocarcinomas and occur early during tumorigenesis. Activating mutations in KRAS result in constitutive activation of the MAPK pathway via RAF, MEK, and ERK1/2 resulting in tumor cell survival, growth, and invasion. Efforts to therapeutic target KRAS have

been biochemically challenging and continue to be the source of fervent preclinical studies and early phase clinical trials. A novel, propriety polymetric matrix used to encompass a siRNA targeting the KRAS G12D, the most common point mutation seen in pancreatic cancer, is currently under active investigation. This complex, named siG12D-LODER, has shown favorable pharmacokinetics, safety, and efficacy (with local administration) in preclinical models [13]. Results from a first in human phase I study of siG12D-LODER combined with weekly gemcitabine in patients with locally advanced pancreatic cancer showed that the combination was well tolerated with 10 of 12 patients showing stable disease and 7 of 10 patients showing a decline in CA19-9 levels [14]. The PROTACT trial is a phase II study of siG12D-LODER in combination with gemcitabine and nab-paclitaxel and is currently ongoing (NCT01676259).

Two trials initiated by the National Institutes of Health are evaluating the safety and efficacy of utilizing peripheral blood lymphocytes transduced with a murine TCR recognizing mutated KRAS (NCT03745326, NCT03190941). These studies are based on preclinical work that demonstrated adoptive transfer of HLA-A*11 restricted peripheral blood lymphocytes transduced with a murine TCR specific for either KRAS G12D or G12V effectively slowed the growth of pancreatic cancer xenografts [15].

Autophagy

Interestingly, targeting signaling downstream of KRAS with either MEK or RAF inhibitors have not shown clinical efficacy in pancreatic cancer, despite the high frequency of constitutively active KRAS mutations. Recent preclinical data demonstrated that inhibition of autophagy, the process by which cells recycle cellular contents to sustain growth during conditions of stress, may sensitize pancreatic cancer cells to MEK inhibition. Treatment with trametinib (a MEK1/2 inhibitor) led to activation of the LKB1 signaling pathway, a key pathway involved in regulation autophagy, and addition of chloroquine, an inhibitor of autophagy in combination with trametinib led to synergistic inhibition of pancreatic tumor cell growth in vitro and regression of patient derived xenografts in vivo [16]. Similarly, ERK 1/2 inhibition increased autophagy in pancreatic cancer cells, and promoted dependency upon this process for growth and survival in the presence of ERK 1/2 inhibition [17]. Combination therapy with hydroxychloroquine and an ERK 1/2 inhibitor resulted in a synergistic inhibition of pancreatic cancer xenograft growth in vivo [17]. These data demonstrate that pharmacologic inhibition of MAPK signaling in pancreatic cancer cells leads to increased autophagy and that simultaneous inhibition of MAPK signaling and autophagy results in synergic inhibition of pancreatic cancer cell growth.

There are several ongoing early phase clinical trials evaluating the safety and efficacy of simultaneous inhibition of MAPK signaling and autophagy. The THREAD trial is a phase I study evaluating the safety of trametinib in combination with hydroxychloroquine in patients with advanced pancreatic cancer who have progressed on at least one line of therapy (NCT03825289). The combination of binimetinib (a MEK inhibitor) with hydroxychloroquine is being evaluation in a phase I study in patients with metastatic, KRAS-mutated pancreatic cancer (NCT04132505).

Other Targets

Approximately 10% of pancreatic cancers harbor mutations (either germline or somatic) in DNA-damage response (DDR) genes which may preferentially sensitize these tumors to PARP inhibitors [18]. The recent FDA approval of olaparib maintenance therapy in patients with metastatic pancreatic harboring germline BRCA1/2 mutations who have not progressed on platinum based chemotherapy has led to increased interest in combining PARP inhibitors with other treatment modalities that may induce a DNA damage response [19]. The VelGemRad trial is a phase I study evaluating the safety of combining veliparib with gemcitabine and radiation in

patients with locally advanced pancreatic cancer (NCT01908478).

Auroka kinases (AKs) comprise a family of serine/threonine kinases that are overexpressed in various solid tumors, including pancreatic cancer. Expression of AK are mediated in part by MAPK signaling (via ERK1/2) and inhibition of AK using the pan-AK inhibitor alisertib inhibits the growth of pancreatic cancer cells in vitro. Alisertib is being evaluated in a phase I study in combination with gemcitabine in patients with advanced pancreatic cancer (NCT01924260).

P53 is mutated in 50–70% of pancreatic cancer and results in loss of the critical G1 checkpoint during the cell cycle. Cells that undergo DNA damage are halted at the G2/M phase to allow for DNA repair prior to proceeding with mitosis. WEE1 inhibits the activity of cdc2, which prevents progression through the G2 checkpoint. Inhibition of WEE1 sensitizes tumor cells to DNA damaging agents, particularly in p53 mutated tumors since these tumors are dependent on the G2/M checkpoint to prevent programmed cell death [20]. The WEE1 inhibitor MK-1775 is being evaluated in combination with gemcitabine and nab-paclitaxel with patients with advanced pancreatic cancer (NCT02194829).

Conclusions

There continues to be a critical need for novel therapies for the treatment of both localized and advanced pancreatic cancer. A majority of active phase I studies in pancreatic cancer involve some form of immunotherapy, whether it be checkpoint inhibitors, vaccines based approaches, adoptive cellular therapy, or some combination of the above. More of these studies are being done in patients with localized disease, which may offer a longer duration of treatment and higher likelihood of benefit compared to the metastatic setting. Preclinical studies are critical in furthering our understanding of the tumor immune microenvironment and will continue to inform rational combination therapies. Similarly, an advanced understanding of the tumor biology of pancreatic cancer has led to an outpouring of novel targeted agents that are currently being evaluated either as monotherapy or combined with other treatment modalities. Continued scientific advancement coupled with rational trial design, and clinical trial enrollment are requisite in order to transform the treatment landscape of pancreatic cancer.

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25 Mechanisms and Evidence on Pancreatic Cancer Prevention

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Introduction

Pancreatic cancer is one of the most common causes of cancer-related deaths [1]. Given the aggressive nature of this malignancy, several ongoing efforts are aiming for early detection at stages at which surgery could have a curative effect. Recent updated national guidelines continue to advice against screening in the general populations [2, 3]. Several institutions have implemented screening programs on high-risk populations [4], following "Cancer of the Pancreas Screening Study (CAPS) guidelines" [5, 6]. Besides surveillance, not much is available to offer to these patients. Ideally, multi-institutional preventive trials should be initiated in these high-risk populations, but the question is, what agents should be tested?

Several compounds have been associated with a lower risk of pancreatic cancer development. In this review, we explore the evidence associated with pancreatic cancer risk reduction. We have searched for systematic meta-analyses of pancreatic cancer preventive compounds as well as some promising agents recently described as potentially preventive, like antibiotics.

Moreover, we explore the cancer-preventive mechanisms of action, including immunomodulating effects triggered by the agents [7, 8]. Several murine preclinical studies have demonstrated that strategies that target the host immune responses can effectively control tumor onset and progression, ultimately resulting in cancer prevention [9].

Further understanding the agents with the potential to prevent pancreatic cancer could be important for selection of agents for clinical trials in high-risk populations. It is essential to strengthen our perspective on prevention for such aggressive disease with limited treatment options.

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_25

Metformin

General Background and PC Risk Association

This drug, a dimethyl-biguanide, has been in use since the 1950s. It is now the most commonly used oral antidiabetic medication worldwide, which lowers blood glucose levels via decreasing hepatic gluconeogenesis, glycogenolysis, and increasing insulin sensitivity [10, 11]. Several studies have shown a role for metformin in cancer prevention, treatment, and survival in many cancer types including pancreatic, colorectal, liver, lung, and breast cancer [12–16]. Several meta-analyses have been conducted in diabetic patients comparing the risk of pancreatic cancer development in metformin users vs. non-users, and most of them have shown that metformin is associated with reduced risk for pancreatic cancer development [13, 14, 17, 18]. On the contrary, Singh et al. [19] did not find a significant association between metformin use in diabetes patients and pancreatic cancer development, which is attributed to the heterogeneity of studies included. Besides the encouraging data on pancreatic cancer prevention effect of metformin, recent meta-analyses revealed that metformin use is also associated with increased survival in patients with pancreatic cancer [19–23].

Anti-tumoral and Immunomodulatory Mechanisms

Multiple mechanisms for the anti-tumoral effects of metformin have been reported: regulation of adenosine monophosphate-activated protein kinase (AMPK), the mammalian target of rapamycin (mTOR), and insulin/IGF-1 signaling pathways, which result in inhibition of cell growth and angiogenesis and induction of apoptosis, autophagy, and cell cycle arrest [24–28]. Another mechanism involves the induction of energy crisis of cancer stem cell and evasion via an AMPK/mTOR independent pathway [29]. Anti-inflammatory and anti-angiogenic effects have also been reported via the reduction of pro-inflammatory cytokines TNF-α, IL-6, and angiogenic cytokine VEGF [30]. Metformin can suppress tumor growth, invasion, and epithelial-mesenchymal transition by reducing TGF β1 production, Smad2/3 phosphorylation, and distinct microRNA regulated mechanisms [31–33]. Metformin can also modify the tumor microenvironment by increasing recruitment of $CD8^+$T cells, secretion of IL-2, and IFNγ and preventing the exhaustion of tumor-infiltrating lymphocytes [34, 35]. Additionally, metformin is able to inhibit the development of Th1 and Th17 cells, as well as the T-cells production of IL-22 [36]. Metformin's ability to restore major histocompatibility complex- I on cancer cell surface has also been linked to the enhancement of immune recognition [37]. Metformin can also promote senescence-associated secretory phenotype and immune-mediated clearance of senescent cells [38] (Table 25.1).

Clinical Use and Potential for PC Prevention

Regarding the clinical efficacy of metformin in pancreatic cancer, there are few clinical trials performed: A Phase II trial of metformin and paclitaxel for patients with gemcitabine-refractory advanced adenocarcinoma of the pancreas failed to meet the primary endpoint of disease control rate, and the treatment combination was poorly tolerated [39]. Another phase 2 study evaluated the efficacy of adding metformin to the combination of gemcitabine and erlotinib, in locally advanced or metastatic pancreatic cancer with negative results [40]. The study of metformin plus mFOLFOX is completed but results are pending (NCT01666730). Most recently, a phase 1b study of metformin (Met) with rapamycin (Rapa) as maintenance therapy after induction chemotherapy in patients with metastatic pancreatic adenocarcinoma showed that the combination was well-tolerated, and several patients achieved stable disease associated with

Table 25.1 Anti-tumoral and immunomodulatory mechanisms of pancreatic cancer preventive agents

Agent	Tumor preventive mechanisms
Metformin	Regulation of AMPK, mTOR, and insulin/IGF-1 signaling pathways ➔ inhibition of cell growth and angiogenesis, induction of apoptosis, autophagy and cell cycle arrest Energy crisis of cancer stem cell ↓Proinflammatory cytokines TNF-α, IL-6, VEGF ➔ anti-inflammatory and antiangiogenic effects ↓TGF β1 production, ↓Smad2/3 phosphorylation, microRNA regulated mechanisms ➔ suppress tumor growth, invasion and EMT ↑CD8+ T cells via preventing the apoptosis of TIL ➔ modify tumor microenvironment Inhibit naïve CD4 ➔ Th1 and Th17 cells development and ↓IL-22 production ↑MHC-I on cancer cell surface ➔ enhance immune recognition of cancer cells ↑Senescence-associated secretory phenotype and immune-mediated clearance of senescent cells ➔ prevention of malignant and metastatic progression
Statins	AMPK activation and post-transcriptional ↓ HIF-1α ➔ inhibition of angiogenesis Inhibition of Akt/PKB, NFKB, and Raf/MEK ➔ chemotherapy sensitization Inhibition of the mevalonate pathway and reducing the intracellular isoprenoids ↑Dendritic cell activation, inflammasome formation, and caspase-1 activation ↑Secretion of pro-inflammatory cytokines such as IL-18 and IL-1β ➔ NK cell activation in the tumors ↑MHC-I on cancer cells ➔↑NK cell mediated recognition ↑Transporter protein TAP1, co-stimulatory molecules (CD80/CD86) ➔ ↑ CD8+ T cells responses ↑Pro-angiogenic M2-like tumor-associated macrophages ➔ enhances both innate and adaptive immune responses ↑Activation of regulatory T cells ➔ immunosuppressive effect
Aspirin	Modification of COX2 and inhibition of Ras, RAF/MEK/ERK signaling pathway ➔ Carcinogenesis, inhibition of tumor proliferation Inhibition of NF-KB, AMP, mTOR ➔ Inhibition of tumor promoting inflammation Inhibition of prostaglandins ➔ Inhibition of immune escape of cancer cells Inhibition of PGE2 ➔ ↑NK activity, ↑ DC activation, ↑CD8+ T cell activation, ↑IL-2, IFNg, ↓ Foxp3
Vitamin D	↑p21 and p27 expressions, cell cycle arrest at the G1 phase, inhibition of PI3K/Akt pathway, inhibition of Wnt/β-catenin signaling via VDR crosstalk ➔ Antiproliferative effect ↓NF-kB, ↑E cadherin expression and ↓transcription of MMP ➔ inhibition of EMT ➔ ↓ Cellular migration, invasion, metastasis ↓COX-2 expression ➔ ↓ Angiogenesis ↓Proinflammatory response via inhibition of prostaglandin synthesis, p38-MAPK signaling, NF-kB signaling and pro-inflammatory cytokines IL-6 and TNF- α ↓Inflammatory markers and fibrosis in tumor stroma via VDR dependent pathway ↑PSCs in quiescent state➔ induced stromal remodeling supporting anti-tumor effect, ↓tumor volume, chemosensitization and ↑survival
Vitamin C	↑ROS ➔ DNA single-strand breaks ➔tumor cell death ↑ROS ➔ ↑Autophagy via a caspase-independent pathway ↑Mitochondrial damage ➔ ↓ATP production ➔ tumor cell and cancer stem cell energy crisis ↑Immune cell activation via HIF dependent pathway ↑Tumor associated macrophages➔tumor invasion by macrophages ↓Tumor CD8+T cells ↑Th1 cytokines, IL-12p70, and IFN-γ, ↓Th2-cytokines by naive T cells
Vitamin E	↓NF-kB ➔ ↓ Tumor growth ↓Her2/ErbB2 expression ➔ Suppression of PI3 kinase/ AKT/ mTOR signaling and Ras-Raf-MEK-ERK pathway ➔ ↑Apoptosis ↑TNF-related TRAIL-induced apoptosis ↑Ceramide synthesis, inhibition of HMG-CoA pathway, surviving signaling ➔ Initiation of apoptosis ↑Bcl-2-associated X protein and ↑zinc finger transcription factor EGR-1 ➔ Apoptosis induction Inhibition of cancer stem-like cells, migration, invasion, EMT and metastasis RAF-MEK-ERK signaling inhibition, accumulation of p27(Kip1) ➔ G1 cell cycle arrest ➔ ↓Proliferation

(continued)

Table 25.1 (continued)

Agent	Tumor preventive mechanisms
Antibiotics	↑M1 tumor-suppressive macrophages ↓Myeloid-derived suppressor cells ↑TH1 differentiation of CD4+ T cells ↑CD8+ T-cell activation ↑PD-1 expression ↓Immune tolerance generated via selective Toll-like receptor activation in macrophages and T cell anergy ↓Cancer stem cells
Checkpoint Inhibitors	Inhibition of CTLA-4 binding to CD80/86 on APCs ➔Enhancing cytotoxic T cell activation Evasion of PI3K/Akt pathways, cyclin D3, CDK4/CDK6, and NF-κB inhibition ➔ inhibited alteration of T cell differentiation Inhibition of PD1/PD-L1 or PD-L2 binding ➔evasion of downstream TCR signaling ➔ Enhancing T cell anti-tumor activity Inhibition of PD-L1 binding to CD80 on APCs ➔ Inhibition of T cell suppression

an exceptionally long survival [41]. Median progression-free survival (PFS)/ overall survival (OS) were 3.5 (95% CI: 2.9–9.2)/13.2 months (95% CI: 7.8 to not reached), respectively, with 2-year OS rate of 37% (95% CI: 21–66%); there were no differences between treatment arms. The exploratory analysis showed that better survival was associated with low baseline neutrophil to lymphocyte ratio, baseline negative PET, and the expansion of dendritic cells following treatment [41].

Overall, many preclinical studies have looked at the role of metformin on tumor biology. Most of those experiments achieved desirable responses on higher doses than the conventionally used for diabetes treatment. Metformin has minimal side effects profile, and the most common are gastrointestinal side effects [42], the most concerning being lactic acidosis, rarely observed at regular doses [43]. However, using higher than usual doses of metformin in the clinical setting for prevention strategy will raise the concern for lactic acidosis. The retrospective clinical studies are describing controversial results with metformin, the best possible benefit observed only in patients with diabetes. Based on these studies, metformin could be the preferred anti-diabetic agent if the patient has concurrent diabetes and pancreas cancer or high risk of developing pancreas cancer. Lastly, except for the phase 1b study of metformin with rapamycin as maintenance therapy, none of the other reported clinical studies showed benefit with metformin [39–41]. With limited efficacy in clinical trials, we do not have enough evidence to recommend metformin as a chemoprevention agent in high risk patients without diabetes.

Statins

General Background and PC Risk Association

Used as lipid-lowering agents since the 1970s [44], statins' primary mechanism of action is the inhibition of HMG-CoA reductase. Since that time, many other unique effects of the statins have been discovered, including anti-inflammatory, cardioprotective, antiangiogenic, and anti-cancer properties [45–48]. Statins use has been linked to decreased risk of cancer development including pancreatic, colorectal, prostate, and ovarian cancers [49–53] in observational and meta-analyses studies. In contrast, there are two meta-analyses in the literature investigating the effect of statin on pancreatic cancer risk that were not able to show a statistically significant decrease in pancreatic cancer development rates in patients using statins [54, 55].

Anti-tumoral and Immunomodulatory Mechanisms

The anti-tumoral effects of statins have been investigated for the past three decades. Statins are capable of reducing pancreatic cancer cell invasion and metastasis as they can suppress cell cycle progression and induce apoptosis [56–58]. High-dose statins can also block angiogenesis via activation of AMPK and post-transcriptional downregulation of HIF-1α [59]. In addition, statins have been found to sensitize to chemotherapy via inhibition of Akt/PKB, NFKB, and Raf/MEK survival pathways [60].

Another important anti-cancer effect of statin is via inhibition of Ras signaling pathway, via mevalonic acid, vital pathway in pancreatic carcinogenesis [61]. Inhibition of the mevalonate pathway and reduction of intracellular isoprenoids causes dendritic cell activation, inflammasome formation, and caspase-1 activation, eventually resulting in tumor-infiltrating NK cells activation [62, 63].

Statins can also cause MHC-I upregulation on tumor cells and NK-cell mediated recognition [64]. In combination with IFNγ, statins can upregulate transporter protein TAP1, and co-stimulatory molecules (CD80/CD86) to potentiate cytotoxic T cell responses [65]. Statins inhibit several pro-inflammatory factors, reducing the formation of immunosuppressive M2-like tumor-associated macrophages, thus enhancing both innate and adaptive immune responses [66, 67] (Table 25.1).

Clinical Use and Potential for PC Prevention

A meta-analysis that was done to evaluate the efficacy of statin treatment in pancreatic cancer patients showed a substantial survival benefit for pancreatic cancer patients [21]. However, a randomized, double-blind, placebo-controlled Phase II Trial of simvastatin + gemcitabine did not show any clinical benefit with adding low dose simvastatin to gemcitabine, although it did not result in increased toxicity [68].

Adverse muscle events, including myalgia, spasms, elevated CK [69], and hepatic dysfunction [70] are the known class-related adverse reactions with the statin. Given the controversial results in the retrospective analysis, negative results in the randomized clinical trial with gemcitabine, and known toxicities of statin medication, there is not enough substantial evidence to recommend statins as a preventive agent in high-risk populations at this time.

Aspirin

General Background and PC Risk Association

Aspirin is one of the most commonly used medications worldwide. It belongs to the family of salicylates that share salicylic acid as their common active agent. In large cardiovascular preventive trials, aspirin has been linked to cancer risk reduction. The Nurses' health study (1980–2010) demonstrated 19% lower risk for colorectal cancer and 15% lower risk for any GI cancer with low dose ≤100 mg regular use of aspirin for a minimum of 6 years [71, 72] The effect of aspirin intake in pancreatic cancer risk remains controversial. A recent meta-analysis indicates a marginal association between high dose of aspirin intake and decreased risk for pancreatic cancer [73]. Other epidemiological studies have reported that regular low- dose aspirin use may reduce pancreatic cancer risk by almost half [74].

Anti-tumoral and Immunomodulatory Mechanisms

Aspirin acetylates the enzyme COX1 leading to its irreversible inhibition and also modifies the enzymatic activity of COX2 [75–77]. The COX2 isoform is involved in inflammatory and carcinogenic processes and influences different path-

ways such as RAS [78]. Additionally, aspirin inhibits COX- independent targets such as NF-KB, activated protein kinase (AMP) and the mechanistic target of rapamycin (mTOR), all signaling pathways associated with tumor-promoting inflammation [79, 80].

Aspirin can target the RAF/MEK/ERK signaling pathway, which is essential for pancreatic precursor lesions formation and tumor proliferation through inhibition of RAF phosphorylation, which leads to RAS/RAF dissociation [81, 82]. Aspirin enhances anti-cancer immunity by inhibiting prostaglandins since overexpression of these molecules has been associated with pancreatic cancer cells escape from the immune system [83–85]. Prostaglandin-E2 (PGE2) protects cancer cells from lysis and attack of natural killers and decreases dendritic cell activation leading to dampened activation of CD8 + T cells [86, 87]. PGE2 is also known to inhibit the production of cytokines IL2 and IFNγ [88].

Aspirin can also inhibit the formation of thromboxane A2, an inducer of platelets activation. Emerging studies have described the role of platelets in tumor initiation, growth, and metastasis. Crosstalk between platelets and cancer cells trigger platelet granule and extracellular vesicles release, which in turn confer antiapoptotic and angiogenic properties to the cancer cell reinforcing tumor growth [89, 90]. Additionally, these factors induce phenotypical changes that favor epithelium to mesenchymal transitions and thus enhances their metastatic potential [91]. These findings suggest that targeting platelets may represent one of the cancer-preventive mechanisms of low-dose aspirin (Table 25.1).

Clinical Use and Potential for PC Prevention

Aspirin is used for the treatment of several conditions such as fever, pain, inflammation, cardiovascular conditions and has been studied for prevention of several types of cancer [71, 92, 93].

Aspirin is a potential chemopreventive strategy for PDAC with promising immunomodulatory properties, but potential side effects such as major GI bleedings and hemorrhagic strokes cannot be ignored, particularly if the drug has to be taken for long time [94, 95]. Current efforts are oriented to develop new derivatives with less gastric toxicity such as Nitric Oxide Aspirin (NO-Aspirin), phospho-Aspirin, glucose-aspirin [96, 97].

Vitamin D

General Background and PC Risk Association

Vitamin D, the precursor of the steroid hormone calcitriol (1,25 dihydroxyvitamin D3 (1,25(OH)2D3), has drawn attention to cancer prevention studies in the last two decades. Several epidemiological and observational studies have shown an association between decreased vitamin D levels and increased risk of several cancer types including breast, pancreatic, colorectal, lung, and bladder cancers [98–102]. Despite this, some meta-analyses did not show a strong association between vitamin D levels and cancer risk reduction [103, 104]. There are four meta-analyses to date examining the association between vitamin D level and pancreatic cancer risk. While three of them did not show significant association between vitamin D levels and pancreatic cancer risk, Liu et al. demonstrated that vitamin D intake can decrease pancreatic cancer risk by 25% [105–108]. The discrepancies among their conclusions were attributed to differences in vitamin D dosages, and the inclusion of high-risk individuals.

Anti-tumoral and Immunomodulatory Mechanisms

Several mechanisms are involved in the anti-cancer effect of vitamin D [109–111], including up-regulation of p21 and p27 expressions, cell cycle arrest at the G1 phase [112], inhibition of

the PI3K/Akt pathway [113], and inhibition of Wnt/β-catenin signaling via decreasing density lipoprotein receptor-related protein 6 (LRP6) levels and vitamin D receptor (VDR) crosstalk [114]. It is also shown to decrease cellular migration, invasion and metastasis via several mechanisms including the inhibition of epithelial-mesenchymal transition (EMT) with suppression of NF-kB, upregulation of E cadherin expression and reduced transcription of matrix metalloproteinases [115]. It is also suggested that Vitamin D decreases angiogenesis via diminished Cox-2 expression causing decreased tumor vascularization [116].

Vitamin D is also capable of inhibiting pro-inflammatory pathways linked to tumorigenesis: prostaglandin synthesis, p38-MAPK signaling, NF-kB signaling, and pro-inflammatory cytokines such as IL-6 and TNF-α [117–120]. Vitamin D can also reduce inflammatory markers and fibrosis in tumor stroma via VDR dependent pathway. VDR is able to regulate pancreatic stellate cells (PSCs) at the transcriptional stage, driving them to a quiescent state, which results in induced stromal remodeling supporting the anti-tumor effect, diminished tumor volume, chemosensitization, and increased survival [121] (Table 25.1).

Clinical Use and Potential for PC Prevention

Currently, several clinical trials are evaluating the efficacy and survival benefit of vitamin D derivative paricalcitol in metastatic pancreatic cancer patients in combination with standard chemotherapy (NCT02030860, NCT03415854) as well as immunotherapy (NCT03331562).

Excessive daily uses of vitamin D can cause hypercalcemia and hypercalcemia-related other side effects, including nephrocalcinosis, arrhythmias, and neuropsychiatric manifestations [122]. Retrospective data on the role of vitamin D in pancreatic cancer prevention is controversial, and the results of clinical trials testing the efficacy of vitamin D in combination therapies are pending. Further chemopreventive prospective studies vitamin D analogs are needed before any clinical recommendations can be done.

Vitamin C

General Background and PC Risk Association

Vitamin C, ascorbic acid, is a water-soluble, essential nutrient with antioxidant and immunomodulatory functions [123, 124]. Several observational and preclinical studies have shown that vitamin C has anti-tumoral effects in several cancer types, including pancreatic cancer. Several meta-analyses have found an association between vitamin C intake and pancreatic cancer risk reduction [125, 126]. Despite this, Hua et al. [127] did not find a statistically significant relationship between vitamin C and pancreatic cancer risk.

Anti-tumoral and Immunomodulatory Mechanisms

Antioxidant and metabolic mechanisms have been implicated in the anti-tumoral effect of vitamin C. High doses of vitamin C can diffuse into the extracellular fluid and form reactive oxygen species with hydrogen peroxide that can cause tumor cell death through DNA single-strand breaks, which ultimately activate poly ADP-ribose polymerase (PARP) for repair [128]. Ascorbate-induced reactive oxygen species can also induce autophagy through a caspase-independent pathway [129, 130]. Vitamin C also decreases ATP production via mitochondrial damage which can lead to tumor cells energy crisis [131]. This inhibition of energy metabolism pathway has been postulated as a mechanism of specifically targeting cancer stem cells [132].

Vitamin C has immunomodulatory properties, including hypoxia-inducible factors (49)-dependent immune cell activation [133]. HIF1/2 activation increases tumor-associated macrophages formation from ascorbic acid abundant mono-

cytes and causes tumor invasion by macrophages and suppression of tumor cytotoxic T-cells [134, 135]. After being exposed to ascorbic acid-stimulated dendritic cells, naive T cells produce more Th1 cytokines, IL-12p70, and IFN-γ and fewer Th2-cytokines in response to an LPS challenge [136, 137] (Table 25.1).

Clinical Use and Potential for PC Prevention

Vitamin C is a water-soluble vitamin with a safe side effect profile. High doses of daily vitamin C in grams doses have shown to be associated with diarrhea, bloating, and oxalate nephrolithiasis in men [138, 139]. High doses of vitamin C in Phase I/II trials are well tolerated in pancreatic cancer patients [140–143], and further efficacy trials are underway. Vitamin C is a promising pancreatic cancer chemopreventive agent with encouraging clinical data and well tolerability even at high doses. We encourage prospective chemopreventive studies for prevention in the high-risk population.

Vitamin E

General Background and PC Risk Association

Vitamin E is an antioxidant that consists of four tocopherols and four tocotrienols. Recent meta-analyses have shown that higher vitamin E levels are associated with decreased risk of several cancer types including lung, colorectal, pancreas, and kidney [144–147]. Two studies that have examined case controls and cohort studies reported an inverse relationship between pancreatic cancer risk and vitamin E intake [125, 146].

Anti-tumoral and Immunomodulatory Mechanisms

Tocotrienols have shown to be better in anti-cancer functions than tocopherols. They suppress the activity of the transcription factor NF-κB reducing tumor growth in vivo at non-toxic dietary levels [148] and can also sensitize pancreatic cells to gemcitabine (Husain et al., 2011). Other mechanisms include the induction of apoptosis by suppression of PI3 kinase/AKT/mTOR signaling and Ras-Raf-MEK-ERK pathway via downregulation of Her2/ErbB2 expression [149]. Francois et al., 2019 has determined that δ-, γ-, and β-tocotrienol can enhance pancreatic cancer cell tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced apoptosis via degradation of cellular FLICE inhibitory protein (FLIP) [150]. Initiation of apoptosis by γ-tocotrienol can also be upregulated via ceramide synthesis and transport as well as inhibition of HMG-CoA pathway [151]. The enhancement of expression of Bcl-2-associated X protein and direct activation of zinc finger transcription factor EGR-1 have been postulated as another mechanism of apoptosis [152].

γ-tocotrienol can inhibit pancreatic cancer stem-like cells, migration, invasion, epithelial-to-mesenchymal transition, and metastasis of pancreatic cancer cells [153].

While most of the anti-cancer effect of vitamin E comes from tocotrienols, a study has shown that analog of vitamin alpha-tocopherol, vitamin E succinate can induce apoptosis via inhibition of survivin signaling [154] (Table 25.1).

Clinical Use and Potential for PC Prevention

In a phase I trial examining the safety, tolerability, pharmacokinetics, and apoptotic activity of the vitamin E in resectable pancreatic cancer patients, vitamin E proved to be well tolerated even at high doses. No toxicities were seen in doses up to 1600 mg daily, and diarrhea was the only side effect at 3200 mg daily uses [155]. Increased apoptosis of pancreatic cancer cells was also observed in patients with vitamin E treatment [155]. In light of previous clinical and preclinical data, safety, and tolerability of vitamin E, we recommend prospective preventive trials testing vitamin E as a potential effective preventive agent for pancreatic cancer.

Antibiotics

General Background and PC Risk Association

The role of microbial dysbiosis in carcinogenesis has been proposed in several tumor types, including pancreatic, hepatobiliary, lung, and colorectal cancer [156]. Site-specific microbial populations have been identified and associated with an increased risk of pancreatic cancer development. Porphyromonas gingivalis and A. actinomycetemcomitans are bacteria found as part of the oral microbiome and found to be associated with increased pancreatic cancer risk. Bacteria have been found in pancreatic tumors, and its higher diversity has been correlated with better outcomes [157–160].

Anti-tumoral and Immunomodulatory Mechanisms

Mice genetically engineered to develop pancreatic premalignant lesions and cancer have delayed tumorigenesis when rederived in a germ-free environment, and this effect is rescued when mice receive fecal transplantation from mice with cancer [161]. Furthermore, microbes ablation by antibiotics is associated with decreased tumor growth rate and size [161–163]. Antibiotics-mediated ablation of bacteria causes reprogramming of tumor-associated macrophages to M1 tumor-suppressive macrophages and inhibits myeloid-derived suppressor cells. It also enhances the TH1 differentiation of CD4+ T cells, CD8+ T-cell activation, and PD-1 expression. On the other hand, microbial ablation attenuates the immune tolerance generated via selective Toll-like receptor activation in macrophages and T cell anergy [159, 161].

Gammaproteobacteria, which has been found prevalent in pancreatic tumors, has also been linked to chemoresistance via transforming gemcitabine to its inactive form. Antibiotic treatment, mostly by local delivery, reversed this effect, and enhanced the gemcitabine effect [158]. Mitochondrial targeted antibiotics, including erythromycins, tetracyclines, glycylcyclines, and chloramphenicol, have been found to eradicate cancer stem cells as a microbiome independent effect [164].

Recently, fungal species have been detected in pancreatic tumors, and antifungal agents, amphotericin B, and fluconazole have shown to delay tumorigenesis in mouse models [165] (Table 25.1).

Clinical Use and Potential for PC Prevention

Long-term antibiotic use for cancer prevention comes with multiple challenges and disadvantages. Long term used of antibiotics can cause drug toxicity, crossed resistance, and favor the emergence of multi-resistant organisms. The potential adverse effects are broad as they can affect every organ system in various severities from mild drug eruption to acute kidney injury and altered mental status [166].They can alter intestinal microbiota for up to a year [167] or cause selection of pathogenic organisms such as clostridium difficile, causing severe diarrhea [166]. We still have limited evidence regarding the efficacy of antibiotics in pancreatic cancer treatment and prevention. Therefore, considering the serious potential side effects of the antibiotics, we need more information about their effect in combination with chemotherapies and/or immunotherapy.

In the context of PC prevention, antibiotics cannot be yet recommended or suggested for testing in the clinical setting given the long-term requirement unavoidable linked to toxicities.

Immune Checkpoint Inhibitors

General Background and PC Risk Association

Checkpoint inhibitors target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and

programmed death-ligand 1 (PD-L1), eliminating the inhibitory signals on T cells, and promoting cytotoxicity against tumor cells. Given the short time in which these drugs have been available, no studies have yet reported association of these drugs with cancer risk.

Anti-tumoral and Immunomodulatory Mechanisms

CTLA-4 is expressed by T cells and suppresses the activation of cytotoxic T cells in the lymph nodes during the early stages. Two signals are required to activate T cells. Antigen-presenting cells (APCs) express major histocompatibility complexes (MHCs) that bind to T cell receptors (TCRs), generating the first activation signal. CTLA-4 inhibits the second signal via competing with the costimulating receptor CD28 for binding to CD80/86 ligands on APCs. Additionally, this cycle enhances the T cell surface expression of CTLA-4 [168–171]. CTLA-4 was also found to alter T cell differentiation by inhibiting PI3K/Akt pathways, cyclin D3, CDK4/CDK6, and NF-κB [172–174]. Antibodies such as ipilimumab inhibiting CTLA-4 reverse the above-mentioned roles of CTLA-4, facilitating cytotoxic T-cell activation. CTLA-4 inhibition can also lead to depletion of regulatory T-cells within the tumor, enhancing antitumor activity [175]. Tumor cells have also shown to be capable of expressing CTLA-4 and are associated with improved survival in response to immune checkpoint inhibitors [176, 177].

PD-1 is expressed on activated T cells, B cells, and natural killer cells, whereas PD-L1/L2 can be expressed by APCs, exhausted T cells, and tumor cells [168, 170, 171, 178]. PD1/PD-L1 or PD-L2 play a central role in peripheral suppression of T cells by inhibition of downstream TCR signaling [178]. PD-L1 was also shown to induce T cell suppression via binding CD80 on APCs [171]. Inhibition of PD-1 or PD-L1 via checkpoint inhibitors, such as nivolumab, pembrolizumab, or durvalumab, enhances the T cell-mediated antitumor activity [171, 179] (Table 25.1).

Clinical Use and Potential for PC Prevention

Several immune-checkpoint inhibitors have been approved to date for treatment of various cancer types [180]; however, monotherapy studies failed to show efficacy in pancreatic cancer [181, 182] except for a very small subset of patients with mismatch repair deficiency [183]. The characteristic immunosuppressive tumor microenvironment and low quality of tumor antigens are some of the suggested reasons for the poor immune checkpoint inhibitor efficacy [184, 185]. Preclinical studies have focused on the mechanisms of immune checkpoint inhibitor resistance and combination therapies are now being tested targeting CXCL2, CD40, CSF1/CSF1R, and cholecystokinin receptor, to evade this resistance [186–189].

Recently, in a study comparing single-cell transcriptomes of low-grade intraductal papillary mucinous neoplasms (LGD-IPMNs), precursor lesions of pancreatic cancer, high-grade IPMNs (HGD-IPMN), and pancreatic ductal adenocarcinoma tumor samples revealed progressive changes in the tumor microenvironment. While low-grade IPMNs had a proinflammatory tumor microenvironment including cytotoxic T cells, activated T-helper cells, and dendritic cells, as the tumor progressed immunosuppressive microenvironment took over with the infiltration of myeloid-derived suppressor cells and depletion of cytotoxic T cells [190]. This data suggests the possibility of better efficacy of immune checkpoint inhibitors in high-risk patients or patients with IPMN in the setting of a proinflammatory tumor microenvironment.

Given the lack of efficacy of immune checkpoint inhibitors in pancreatic cancer as monotherapy, and the fact that combination therapies would not feasible for long-term prevention

purposes, given toxicity and cost, the use of immune checkpoint inhibitors for pancreatic cancer prevention does not seem promising.

Conclusions and Perspective

Several compounds that are strongly associated to pancreatic cancer risk reduction have been explored. The CAOS study (NCT04245644) has been recently initiated and aims to assess the efficacy of aspirin, statins, metformin, angiotensin-converting enzyme inhibitors, and beta-blockers, on disease-free and overall survival in patients with pancreatic ductal adenocarcinoma. The study will include patients taking any of the above-listed medications regularly who underwent primary chemoradiotherapy or surgical resection, followed by adjuvant therapy or preceded by neoadjuvant chemoradiotherapy. The CAOS study may alleviate the chaos in the setting of secondary prevention, however, mechanisms might be different in primary prevention. To this end, we believe that efforts should be placed in designing short-term preventive trials in high risk populations. Given the low incidence of the disease, studies should assess biomarkers modulation rather than cancer incidence [5, 6, 191]. Patients with high-risk pancreatic cysts also represent a good target population for prevention studies since cystic fluid could serve for biomarkers determination.

In the near future, with more sensitive imaging methodologies and novel specific and sensitive blood biomarkers, preventive studies for pancreatic cancer could be a reality. Until then, better understanding of the mechanisms of action of those compounds and preclinical testing in spontaneous mouse models will aid the development of biomarkers for these types of trials.

Financial Support Dr. McAllister was supported by the Paul Calabresi K12 clinical scholarship (NCI grant awarded to MDACC K12CA088084-16A1), Sabin Award, V Foundation Fellowship, and American Gastroenterological Association.

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Nutrition in Pancreatic Cancer

26

Maria Q. B. Petzel and Chelsea S. Ebrus

Introduction

Individuals with pancreatic cancer (PC) are at high risk for nutrition problems due to tumor anatomical location and its potential effects on endocrine, exocrine, and biliary function. Nutrition status may be affected by the cancer itself or the treatments. Even in the absence of symptoms, altered nutrition needs, or impaired GI function, patients and family members will seek guidance regarding nutritional issues in pancreatic cancer. The goals of providing medical nutrition therapy are to prevent or reverse poor nutrition, maintain weight and strength, manage side effects, maintain dose and schedule of cancer treatments, and improve surgical outcomes.

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Malnutrition, Cachexia, and Sarcopenia

The nutrition status of patients with pancreatic cancer (PC) can vary with stage of disease [1] and change through the continuum of care [2]. Malnutrition is reported to occur in 50–90% of patients with pancreatic cancer [1, 3, 4]. Factors that contribute to malnutrition in PC patients include age, diabetes, anorexia, pain, cachexia, malabsorption, and poor mobility [5, 6]. Though, the exact incidence is thought to have variability, due in part to a historical lack of definition of malnutrition.

The prevalence and degree of cachexia can vary among different cancer types and sites [7, 8]. Incidence of cancer cachexia is highest in patients with gastric and pancreatic cancer [4, 7]. Cachexia is estimated to be present in over 85% of pancreatic cancer patients, with 30% of pancreatic cancer deaths due to cachexia alone [9].

Malnutrition and cachexia are associated with decreased survival, treatment tolerance and response, quality of life, and performance status as well as increased postoperative length of stay, hospital admission/readmission, and post-surgical infection [3, 4, 10–13]. Sarcopenia has been shown to negatively affect survival in both metastatic and resectable PC and is associated with reduced adherence to treatment dose and increased toxicities [14]. Understandably, weight stabilization is associated with improved survival,

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_26

improved QOL, and better surgical outcomes [15–17]. Though neoadjuvant treatment may be associated with decreased nutrition status before surgery, it is not correlated with any difference in complications, LOS, or time to adjuvant treatment [18].

Because of its detrimental nature, detecting cachexia and maintaining muscle mass is a major goal throughout the care of cancer patients [19]. Although weight loss is the main clinical presentation of cachexia in this population, it is the loss of skeletal muscle alone that has the greatest negative impact on physical function, quality of life, and reduced tolerance to anticancer therapies [7, 8, 13, 19].

Cachexia

Cachexia is a complex and challenging syndrome present in many patients with cancer. In 2011, a panel of experts headed by Fearon formally defined cancer cachexia as a syndrome characterized by a loss of skeletal muscle mass, with or without loss of fat mass, that cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment [13]. These experts describe cancer cachexia as a three-stage continuum with increasing severity (Table 26.1) [13].

Cancer cachexia is multifactorial—inadequate food intake, altered metabolism, and ongoing systemic inflammation can all contribute to the process. Side effects of cancer treatment (nausea, vomiting, early satiety, taste changes, generalized loss of appetite) along with mechanical barriers (obstruction in the GI tract) can contribute to inadequate food intake during cancer treatment. Altered metabolism and systemic inflammation often coexist, and can occur due to the disease process of cancer, as well as cancer treatment, whether surgical or medical. Metabolic and systemic changes that are present in this condition are increases in resting energy expenditure, catabolism, and overall inflammation, with increased levels of pro-inflammatory cytokines [7, 20]. In PC patients high levels of inflammatory cytokines and imbalanced peripheral blood mononuclear cells correlate with decreased survival [1].

Although non-definitive, various biomarkers have been notable in detecting and predicting cachexia. Serum CRP is an important biomarker of inflammation and even cachexia, however, it is important to note that cancer cachexia can be present in the absence of systemic inflammation [13]. Pro-inflammatory cytokines are drivers of cancer cachexia [9], and therefore may be useful identifiers of the condition. Specific cytokines commonly increased in pancreatic cancer patients with cachexia are interinterleukin-6 (IL-6) and tumor-necrosis factor alpha (TNF-α), which activate signaling pathways that contribute to muscle wasting and fat wasting [9, 21]. These cytokines are also thought to contribute to anorexia by disrupting the ability of the hypothalamus to send an appropriate response to increase intake of food [9]. Emerging literature suggests that there may

Table 26.1 Cancer cachexia stages, criteria, and management

Cancer cachexia stage	Precachexia	Cachexia	Refractory cachexia
Criteria for stage	• Weight loss ≤5% • Anorexia and metabolic change	• Weight loss >5% • Or BMI <20 and weight loss >2% • Or sarcopenia and weight loss >2% • Often reduced food intake and systemic inflammation	• Cancer procatabolic and nonresponsive to treatment • Low performance status (WHO score 3 or 4) • <3 months expected survival
Management	• Monitor • Preventative intervention	• Multimodal management, with prioritization of reversible factors	• Symptom palliation, psychosocial support • Consider risks/benefits of nutrition support

BMI body mass index
Adapted from Fearon et al. [13]

be additional underutilized markers to predict cancer cachexia, specifically CXCL-16 and IL-1b, but more research is needed in this area [22]. In patients with pancreatic cancer, pancreatic cancer cells themselves also produce these cytokines [4].

Sarcopenia

There remains a lack of consensus definition of cancer-related sarcopenia but it is associated with muscle wasting as well as loss of strength and function of the muscle even in the absence of wasting. Though most patients with cachexia are sarcopenic, sarcopenia may be present without cachexia. Muscle weakness (or decreased muscle density, myosteatosis) may be a risk factor for complications, prolonged recovery, hospitalizations, and compromised quality of life in PC patients following surgery [14].

In a retrospective review of data and images in 78 patients referred for neoadjuvant treatment, 51% presented with low muscle mass and 73% experienced loss of lean tissue during treatment. Muscle loss was associated with greater mortality risk [23].

Nutrition Screening

Nutrition screening should be performed using a validated tool at presentation and at regular intervals over the course of treatment. Nutrition screening should be completed in both hospital and outpatient settings. There are five screening tools validated for use in oncology: Malnutrition Screening Tool for Cancer Patients, the Malnutrition Universal Screening Tool, the Malnutrition Screening Tool (MST), the Patient-Generated Subjective Global Assessment (PG-SGA) (standard and short-form), and the NUTRISCORE tool [24].

There are many other screening tools that have also been used in studies of oncology patients but have not been validated. Probst et al. evaluated 11 tools to determine which had the greatest association between malnutrition and pancreatic surgery complications. Scores varied greatly identifying 1.0–79.6% of patients at risk of malnutrition however none of the tools showed a significant association with major complications in whole group or in subgroup by surgical procedure [25].

Routine nutritional screening using screening tools can identify malnutrition, cachexia, or risk thereof. Assessment by a registered dietitian can identify early stages of cachexia and potentially modifiable factors that contribute to the condition—food intake, catabolic drive, muscle mass, and physical function [13]. In the precachexia and cachexia stages, these factors should be addressed, and nutrition counseling should focus on recommendations for increased energy intake including energy-dense foods, a protein-rich diet (with specific calorie and protein goals), potentially increased meal frequency, and oral supplementation of nutrients.

Malnutrition, Cachexia, and Sarcopenia Interventions in Pancreatic Cancer

The best treatment strategy is to identify patients in the precachexia or cachexia phases and implement early intervention to keep the condition from progressing. It is suggested that pancreatic cancer patients should receive nutritional counseling by a registered dietitian from the time of diagnosis [4, 5]. Management of cancer cachexia, sarcopenia, and malnutrition in pancreatic cancer patients should be individualized and depends on the degree of cachexia. Stabilization of weight but more importantly, the reversal of muscle wasting should be the ultimate goal in cachexia interventions [19, 26].

In a study of patients with unresectable disease median survival was significantly longer in weight-stable vs. weight-losing subjects (8.6 versus 5.5 months). Participants did not receive anticancer therapy during the study, were given oral nutritional supplements, and had a weekly phone call with a registered dietitian for 8 weeks to discuss pain, nausea, pancreatic enzyme replacement therapy (PERT) optimization, and nutrient dense meals [15].

In cachectic pancreatic cancer patients, caloric supplementation has demonstrated a consistent benefit of nutrition supplementation for patients with pancreatic cancer in the form of decreased of loss of muscle tissue and increased survival time, regardless of nutritional product used [4]. Several dietary supplements have been used in the treatment of cancer cachexia in pancreatic cancer patients—Omega-3 fatty acids, L-carnitine, BCAA, and lactoferrin—however, research on these nutrients has not yielded clear and consistent practice recommendations [4]. Clinicians should guide patients in selecting a nutritional supplement and urging consistent use.

Specific to the pancreatic patient, optimization of PERT in those who require it is essential to ideal digestion and absorption, as is ensuring optimal mechanical digestion (see section PERT).

Multimodal interventions including nutrition and exercise components for treatment of cachexia show promise. Combined with nutrition interventions, exercise is recognized as a therapeutic approach to cachexia for preserving muscle mass and performance. This is due to its anti-inflammatory effect along with the repeated stimulation of muscle synthesis that occurs with exercise [7, 27]. Other benefits of exercise in cancer patients include reduced depression and increased anabolic hormones [7]. Exercise has shown positive effects mostly in early stages of cancer. While standardized recommendations for exercise in pancreatic cancer patients with cachexia do not exist, clinicians should recommend both aerobic and resistance training exercise as tolerated, taking into consideration patients' overall physical function [27].

There have been no effective medical interventions to completely reverse cancer cachexia, and currently there are no approved drug therapies for its treatment [1, 7, 20]. Appetite stimulants can be beneficial in improving food intake in affected patients. Of available appetite stimulants megestrol acetate (Megace) has been FDA approved for AIDS-associated cachexia only, with its effectiveness in weight gain being controversial, as it is thought to be due to increased fat/fluid without significant increases in muscle gain [7]. Nonetheless, it has shown superior to other drugs in terms of efficacy and tolerability for the effect of appetite stimulation. Other promising pharmacological agents to manage cancer cachexia are under development—namely ghrelin analogs and selective androgen receptor modulators (SARMS)—but none are widely in use at this time.

Nutrition Intervention

Energy dense, high fat foods, and medical food supplement drinks are often recommended to increase calorie intake in patients with cancer, but patients with pancreatic cancer may not tolerate high fat food or calorie dense oral nutrition supplement drinks. Pancreatic cancer and its treatments may require modifications of usual nutrition interventions for nutrition impact symptoms (Fig. 26.1). For patients with pre-cachexia/cachexia there are no special interventions specific to pancreatic cancer but careful attention should be given to optimal management of the side effects unique to pancreatic cancer.

- Schedule oral intake, plan meals/snacks the day before
- Eat small frequent meals (6-8/day)
- Get plenty of fluids
- Limit use/portions of fat (as needed)
- Choose nutrient dense foods
- Be active
- Take pancreatic enzyme replacement therapy (if prescribed)
- Consider regular use of liquid nutrition supplement drinks

Fig. 26.1 General nutrition recommendations for pancreatic cancer patients

Nutrient Needs

Calorie Needs

Studies to determine the energy expenditure in patients with pancreatic cancer show mixed results. Some show patients with pancreatic cancer are hypermetabolic while others show normo- or even hypometabolic needs [28–31]. There are also variable results suggesting that tumor burden may or may not have a significant effect on energy needs [28, 30]. The variation in findings is likely due to the heterogeneity in analysis of the data or how disease burden is determined [28, 30]. Ultimately, the variation in study findings demonstrates the importance of an individualized nutrition assessment.

Because it is not feasible to measure resting energy expenditure via indirect calorimetry on every patient, nor is it commonly available on an outpatient basis, predictions can be made based on body weight. General recommendations for predicting calorie needs of patients with cancer are to initiate nutrition therapy at 25–30 kcal/kg body weight per day (if obese use ideal body weight) and to periodically reassess and adjust based on the clinical effects on body weight and muscle mass [32]. This recommendation correlates with the findings of Sasaki et al. who found via indirect calorimetry that patients with resectable PC, prior to surgery, are normometabolic, requiring about 25 kcal/kg [31].

Protein Needs

There is also an absence of literature evaluating or reporting protein needs in pancreatic cancer patients. General recommended estimates for protein needs for cancer patients is 1–1.5 g/kg of body weight per day. Some individuals may benefit and safely intake up to 2 g/kg while those with acute or chronic kidney failure should not exceed 1–1.2 g/kg/day [32]. Additionally, it is important that individuals distribute protein through the day (25–30 g/meal) to optimize muscle protein synthesis/maintenance [33].

Micronutrient Needs

PC patients can be at increased risk for micronutrient deficiencies due to pancreatic exocrine insufficiency and/or pancreatic surgery, both of which alter digestion and absorption. Strategies for management of malabsorption are discussed below. It is important for pancreatic enzyme replacement therapy to be adequate to ensure maximum absorption of food sources of vitamins. Specific micronutrient alterations are discussed in the Long-term Survival section of this chapter.

Common Nutrition Issues in PC

Nutrition impact symptoms may be present at the time of diagnosis or lead to a diagnosis of pancreatic cancer. Depending on the etiology some symptoms may be reversible such as loss of appetite and weight loss related to bile duct blockage or malabsorption [34, 35] versus irreversible weight loss due to cancer cachexia [13]. Symptoms are more common in individuals with advanced stage disease. Some may develop symptoms related to progression of disease or as a result of anti-cancer treatments or surgery [36, 37]. It is important to impart to patients and families that nutrition strategies for side effects are adjunct to medications.

Diabetes Mellitus and Hyperglycemia

Diabetes mellitus (DM) is reported to be present in about half of patients at the time of PC diagnosis [38]. DM may be a risk factor for or a symptom of PC. Though long-standing type 2 DM is a risk factor for pancreatic cancer, about 50–75% of patients with PC and DM received the diagnosis of DM within 24 months prior to diagnosis of PC [38, 39].

Pre-existing (DM) has been shown to improve, worsen, or remain stable following surgery [38, 40]. It is estimated to worsen in about half of patients following pancreaticoduodenectomy (traditional or pylorus-preserving) (PD) and one-

fourth of patients following distal pancreatectomy (DP) [40]. Authors report improvement in DM following resection—20–57% following PD and 13% following DP had resolution of DM. However, patients with preoperative chronic pancreatitis, long-standing DM, insulin use, previous glucose intolerance, and malignancy were less likely to have resolution [38]. DM may be newly diagnosed after surgery, it is reported that 17–24% of patients are newly diagnosed with DM following pancreatic resection [38, 40]. DM may be more frequently associated with DP than resection of the head of the pancreas [1]. Studies reporting on PD and DP separately find DM newly diagnosed in 15–41% of those following PD and 8–54% following DP [38].

Receipt of formal diabetes education in patients with cancer is associated with better outcomes (fewer hospitalizations, lower health care expenditures, and fewer emergency visits) [41]. Nutrition management of DM varies depending on the side effects or symptoms a patient is experiencing, their stage of disease, and postoperative recovery. In general, patients may be instructed to minimize the use of refined carbohydrates, consume meals and snacks at regular intervals, and to consume meals/snacks with a mix of protein, complex carbohydrates, and fat (as tolerated). However, in patients experiencing side effects or symptoms that reduce or limit oral intake, it is appropriate to be more liberal with the diet and use more aggressive medication or insulin management [42, 43]. Diet and blood glucose targets should be liberalized with progressive disease and older age to achieve a glycosylated hemoglobin (A1C) <8.0% (fasting blood glucose 90–150 mg/dL) [43, 44].

In patients with no evidence of disease and who have completed treatment, carbohydrate counting is appropriate to aid with long-term glycemic control [42, 45, 46] with a goal of a hemoglobin A1c <7% (fasting blood glucose 80–130 mg/dL) without episodes of hypoglycemia [45, 47]. In a study involving total pancreatectomy patients, better long-term glucose control following total pancreatectomy (fasting blood glucose <155 mg/dL and A1c <7%), was associated with better recurrence-free survival and better overall survival [48].

Gastric Outlet Obstruction and Small Bowel Obstruction

Gastric outlet obstruction (GOO) or duodenal obstruction may affect a significant portion of patients with pancreatic cancer (2–25%), although it typically occurs in advanced stages of cancer [49–55]. GOO or small bowel obstruction (SBO) may be due to obstruction by the primary tumor or peritoneal spread of disease resulting in disordered peristalsis and stenosis [55–57]. Symptoms of an obstruction include abdominal pain and/or distention, along with nausea, vomiting (of accumulated food), and early satiety. An obstruction can cause decreased food intake, weight loss, dehydration, and electrolyte imbalances [51–55].

Both gastrojejunostomy and duodenal stenting have been shown to be effective treatments for GOO/SBO, although each do have their benefits and drawbacks. Duodenal stenting results in faster return to oral intake and a shorter hospital length of stay than gastrojejunostomy [54, 58–60]. However, duodenal stents come with higher risk of complications, such as tissue ingrowth into the stent or stent migration. Recurrent obstruction due to these complications has been reported in 17–27% patients with endoscopic stents, indicating potential need for monitoring and repeat intervention long term [54]. Gastrojejunostomy tends to provide longer symptom relief without requiring reintervention, but delayed gastric emptying even after gastrojejunostomy can persist in 30–50% of patients [54, 58, 61].

Sometimes neither duodenal stenting nor gastrojejunostomy are an option due to disease progression or location; in these cases, a gastrostomy tube (g-tube, known in this case as a decompression or venting g-tube) can be inserted into the

stomach for drainage to palliate symptoms [61]. A jejunostomy tube (j-tube) for feeding may also be inserted at the time of gastrojejunostomy or venting g-tube placement [62].

Appropriate diet after duodenal stent or venting gastrostomy tube is lacking a uniform consensus. Individual practice is variable, but in both cases, diet is generally the same. The suggested diet after duodenal stent placement based on current literature is a low fiber/soft diet [51, 63, 64]. Before transitioning to this diet long term, tolerance to liquids should first be established. It should be noted that in some literature and some practices, patients are ultimately advanced to a regular diet. Kobayashi and colleagues [50] utilized a uniform diet progression in practice in which patients consumed a liquid diet on day 1 after stent placement, soft foods on day two, and a regular diet on day 3. With all oral intake, patients should be instructed to thoroughly chew foods and consume ample fluids to achieve a liquid food bolus that travels past the stent with ease.

Recommended diet parameters for patients with decompression gastrostomy tubes are similar to diet modifications with duodenal stents. At some institutions, patients may be instructed to blenderize or puree foods before progressing to a soft diet, although this may be labor-intensive to the patient [65, 66]. Other institutions may allow patients to progress to a regular diet as tolerated [66–68]. Patients should take care to avoid blockage by flushing the tube and avoiding any specific food that causes a blockage episode [67].

Diet modification and bowel management strategies can also be beneficial in patients with advanced stage PC at risk for SBO. McCallum and colleagues found that in such patients, diet education regarding a soft, low-fiber diet can prevent obstruction [57]. In this retrospective review, patients had been instructed to chew food thoroughly and avoid nuts and seeds, peas, beans, lentils, and all raw fruits and vegetables. Of 17 patients who received pre-emptive diet education, none experienced obstruction. Conversely, 12 of 17 patients who did not receive diet education experienced obstruction [57]. This study suggests that patients at high risk for bowel obstruction should be educated regarding a low fiber diet, which should be paired with aggressive bowel management, if indicated.

Delayed Gastric Emptying

Alterations in GI transit time may be due to PC, DM, or surgery. Delayed transit time may present in the form of delayed gastric emptying (DGE) or gastroparesis. Classic PD versus pylorus-preserving (PPPD) have been thought to have different effects on GI transit time. A consensus definition for DGE was published by the International Study Group of Pancreatic Surgery (ISGPS) in 2007 [69]. Using this definition, the incidence of DGE is reported to occur in 15–61% of patients following pancreatic surgery (including DP) [70–77].

A large cohort study by Snyder, Ewing, and Parikh found that of a sample of over 10,000 patients who underwent either form of PD, 16.6% developed DGE [74]. Of this population, those who underwent PPPD represented a slightly larger portion of those with DGE. Similarly, in a Cochrane Review, Huttner et al. found that DGE may have greater incidence in patients with PPPD versus PD, although this was not definitive [78]. This same Cochrane Review found ultimately no significant advantages of PPPD over PD. This is in contrast to prior suggestions that PPPD may give a better quality of life and improved postoperative outcomes [78–83]. Regarding the two procedures, some results are mixed, such as those from a 2018 meta-analysis concluding that ultimately PPPD is not superior unless technically or oncologically indicated [72].

Diet modification to cope with DGE/gastroparesis involves a diet low in fat and fiber, small meals that are frequent (4–6 times per day), ensuring food is well-chewed, and consuming ample fluids with meals. Semi-solid foods and nutrient-dense liquids such as nutritional supplements may be better tolerated [84]. Prokinetic medications such as metoclopramide and erythromycin may be prescribed to aid in

quickening GI transit [85, 86]. Nutrition support may be initiated if a patient is unable to absorb adequate nutrients due to gastroparesis for a prolonged period of time of 7–14 days or more [85–87]. Special attention should be given to glycemic control for patients with DM, as hyperglycemia is a contributing factor to DGE.

Pancreatic Exocrine Insufficiency (PEI)

PEI leading to malabsorption in pancreatic cancer may be due to loss of pancreatic parenchyma, obstructed duct, changes in GI tract synchrony, and/or reduced pancreatic secretions [88, 89]. PEI or malabsorption is reported to occur in 50–100% of PC patients [88, 90, 91]. Patients may present without PEI but develop as disease progresses or due to treatment. One study showed that 66% of patients had PEI at presentation 92% by the end of the 6 months study. PEI may develop or worsen following radiation therapy (RT) [92]. It is reported in 50–100% of patients following PD [1, 2, 93, 94] and in 0–50% following DP [1, 94]. PEI is reported in 20–92% of patients with unresectable disease [93, 94]. These variations in reported incidence are largely related to variation in means (Fig. 26.2) and timing of evaluation. PEI may also be diagnosed based on clinical symptoms (Fig. 26.3), however, exocrine secretions can be reduced without presenting with clinical symptoms therefore if only assessing for clinical symptoms patients may be under (or over) diagnosed [93]. PEI can manifest as symptoms but also a failure to absorb macro- and micronutrients [101]. Consequences of PEI include malnutrition/sarcopenia, nutrient deficiencies including fat-soluble vitamins, serum proteins (albumin, retinol-binding protein, apolipoproteins, high-density lipoproteins, transferrin) and magnesium and zinc. Malabsorption is also associated with increased risk of osteoporosis and low-trauma fractures [93, 95]

Because many of these reports are based on fecal elastase, it is important to consider that accounts of PEI following surgery generally only represent those individuals with reduction in pancreatic exocrine enzyme production or clinical symptoms. Though patients may still have adequate enzyme production (normal FE), the anatomical changes from PD may lead to asynchrony within the gastrointestinal tract, and therefore malabsorption because endogenous enzymes are not meeting food at the appropriate point in the digestive system [89, 94, 97]. Reports of only 50% of patients with PEI post PD are likely under reporting incidence of long-term malabsorption. Surgical reconstruction following PD and PPPD may also influence effectiveness of endogenous pancreatic enzymes. Pancreaticogastrostomy may be performed due to technical reasons during minimally invasive surgery or as a surgeon preference; however, it may lead to increased need for supplemental enzymes as exposure of pancreatic secretions directly to gastric acid will inactivate endogenous pancreatic enzymes [102, 103]

- Abdominal bloating
- Cramping or abdominal pain after meals
- Excessive gas (burping, flatulence)
- Indigestion
- Foul-smelling gas or stools
- Unexplained weight loss
- Stool changes:
    - Fatty or oily (frothy, foamy)
    - Frequent
    - Floating
    - Light-colored or yellow
    - Loose

Fig. 26.3 Clinical symptoms of pancreatic exocrine insufficiency [97–100]

Fig. 26.2 Diagnostic tests for pancreatic exocrine insufficiency [89, 95, 96]

- Coefficient of fat absorption
- Fecal chymotrypsin level
- Fecal elastase (Fecal elastase 1)
- Fecal fat excretion
- Urinary PABA (para-aminobenzoid acid) excretion rate
- 13C-labeled mixed triglyceride breath test

Management of PEI

Pancreatic Enzyme Replacement Therapy

When PEI is present, pancreatic enzymes (pancrelipase (Table 26.2)) should be prescribed. Pancreatic enzyme replacement therapy (PERT) is demonstrated to have a positive effect on body weight, stool frequency, total calorie, and total protein intake even in the absence of symptomatic improvement [109]. It has also been demonstrated to help maintain or improve nutrition status following surgery in 74% of patients [2]. Dominguez-Munoz et al. found in a retrospective analysis of patients with unresectable PC, 3 month greater median survival for patients on PERT vs. no PERT [110]. PERT was also associated with increased survival following PD for periampullary tumors [111].

Despite these benefits, PERT may not be prescribed to the majority of patients who need it [101, 112]. Underutilization of PERT is associated with poorer quality of life [113]. Landers et al. evaluated patients for PEI symptoms, upon referral to hospice, finding only 21% of patients with pancreatic cancer were on PERT whereas 70% of them had symptoms of PEI [112]. In a cohort study of patients with PDAC, Roberts et al. [101] investigated whether PERT was associated with increased survival. Authors matched 807 patients with PDAC who received PERT to 807 non-PERT-treated controls, with no major differences in patient characteristics. The study found median survival was significantly greater among the patients who received PERT, with median survival at 274 days versus 140 days, even when excluding surgical patients and when comparing between groups with or without adjuvant chemotherapy. The study also identified that use of PERT among PDAC patients was low, with only 21.7% of 4554 patients having received PERT at all [101].

Enzymes may be dosed based on an assumed general intake of food at meals and snacks, the patient's body weight, or the fat content of the diet. The most common practice is meal-based dosing. Recommended starting doses range from

Table 26.2 FDA approved pancrelipase brands [104–108]

Brand	Capsule strength (lipase units)	Dosage form
Creon®	3000	Delayed-release capsule, enteric coated spheres/beads/microtablets
	6000	
	12,000	
	24,000	
	36,000	
Pancreaze®	2600	Delayed-release capsule, enteric coated spheres/beads/microtablets
	4200	
	10,500	
	16,800	
	21,000	
Pertzye®	4000	Delayed-release capsule, bicarbonate-buffered enteric coated spheres/beads/microtablets
	8000	
	16,000	
	24,000	
	37,000	
Viokace®	10,440	Tablet—no enteric coating
	20,880	
Zenpep®	3000	Delayed-release capsule, enteric coated spheres/beads/microtablets
	5000	
	10,000	
	15,000	
	20,000	
	25,000	
	40,000	

20,000 to 80,000 lipase units per meal and about half that per snack [2, 10, 42, 88–90, 93, 94, 98, 99, 110, 114]. Enzymes may be titrated up every several days as needed considering the characteristics of stools, clinical symptoms, and nutrition intake ultimately finding the lowest effective dose to most effectively minimize or avoid PEI symptoms [93, 95, 98, 104]. Supplemental pancreatic enzyme dosages should not exceed 10,000 lipase units per kilogram per day or 2500 lipase units per kilogram per meal up to 4 times a day [98].

A wide range of dosing reflects the wide range of diet variation—some patients may present having already self-restricted the fat content of the diet or meal sizes and therefore need lower doses of PERT while other individuals eating regular size meals or large amounts of fat may need higher doses. Though the literature reports a higher range of starting doses, because many patients with pancreatic cancer have reduced food intake either due to symptoms or surgery, it is often more prudent to start at the low end of the range for meal-based dosing rather than the high end [115].

To best mimic the normal physiologic response to eating, the enzyme dose should be divided and administered at the start and throughout the meal, and at the end [42, 98, 116]. See Fig. 26.4 for a guide through the process of starting PERT, titrating dose, and troubleshooting problems.

Variation in content, size of pellets, and dissolution properties of the enteric coating can influence effectiveness of PERT and limits bioequivalence of different brands [93]; therefore, it is recommended for patients to be maintained on the same brand of enzyme (Table 26.2). It is also suggested that some patients may respond differently to equivalent lipase doses but different brands.

Recently, a few studies have been conducted specifically seeking appropriate postoperative dosage. It should be noted that these may be funded in part or full by the manufacturers and evaluated patients a minimum of 1 month following surgery. These randomized placebo controlled studies have demonstrated benefit with taking 40,000–75,000 total lipase units per meal as compared to placebo [95, 117, 118] Benefits included decreased stool frequency by ~1 BM per day and weight maintenance or gain.

PERT Optimization and Troubleshooting

It is important to continue to reassess compliance with enzyme use and recommended dosage throughout the troubleshooting process. Achieving optimal management of PEI often requires close attention to detail that may be optimized through work with a registered dietitian nutritionist [5, 119].

Dunleavy and colleagues [120] found, through qualitative interviews, that few patients had adequate knowledge about enzyme dose titration for general PEI symptom management or for addition of high fat foods. Some participants were continuing to struggle with remembering to take PERT for several months postop, more prominent in men. Symptoms common to PEI may also or alternately be due to other causes (decreased GI transit time, chemotherapy) PERT may not completely resolve these symptoms. For patients with severe PEI, optimizing PERT may not eliminate steatorrhea altogether, but can reduce symptoms significantly (60–70%) [42, 97].

A physiologically basic environment is needed for both enzyme function and bile acids to transport fatty acids into the blood [42, 97]. When pancreatic exocrine function is compromised, it is suggested that an H_2-receptor antagonist or proton-pump inhibitor should be used in addition to PERT because bicarbonate production and transport to the small intestine could be impaired, potentially resulting in decreased PERT effectiveness [93, 116].

Lastly, the cost of enzymes can be burdensome and patients may seek to use an over-the-counter (OTC) preparation or may ration their supply of pancrelipase. OTC enzyme preparations may include bromelain, papain, trypsin, and chymotrypsin or may be a combination product [121]. There is a lack of strong data to support use of these supplements and as with all OTC supplements, individuals

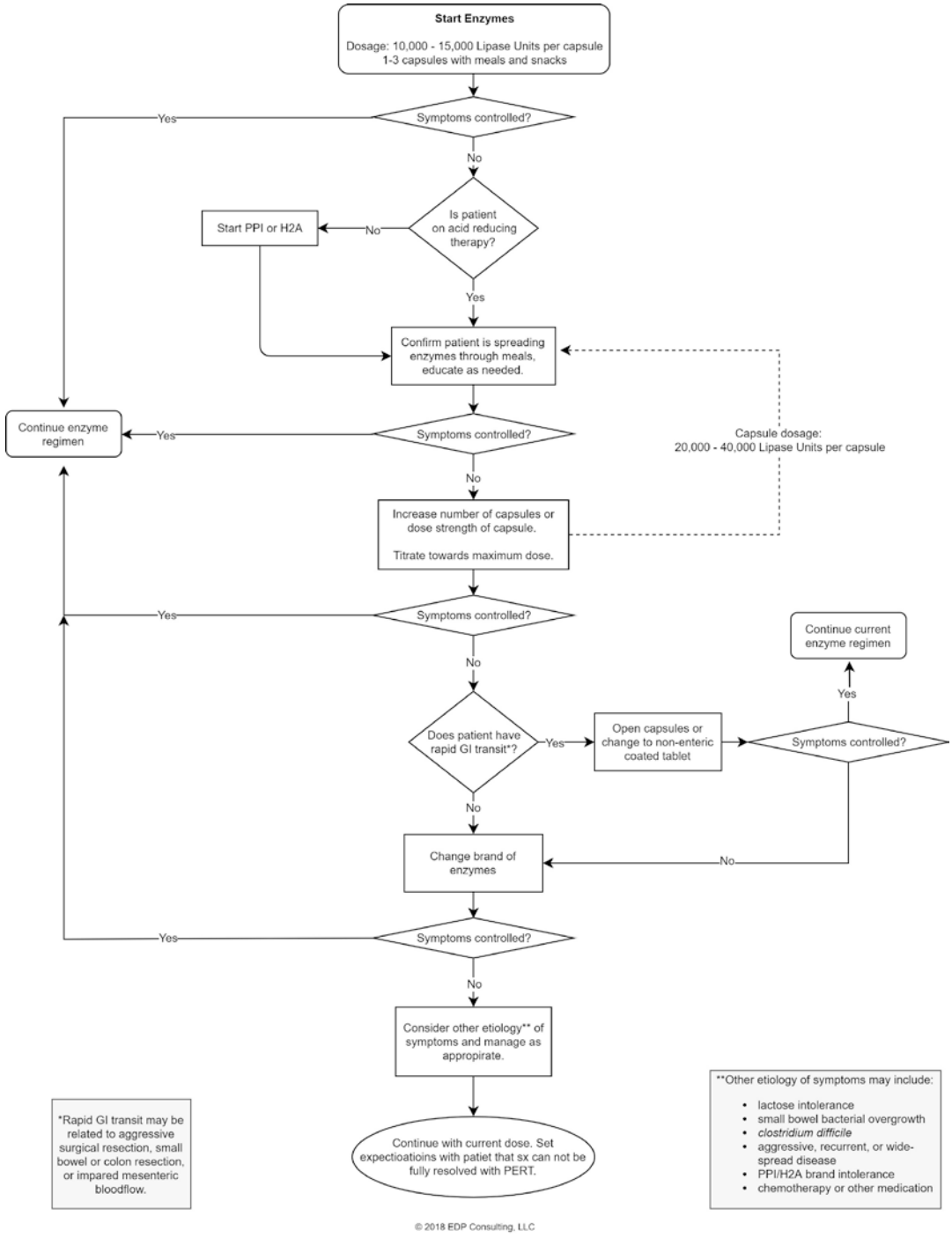

Fig. 26.4 Pancreatic enzyme replacement and optimization (sent as separate file)

should be counseled regarding concerns with the non-regulated industry and potential for non-standardized or appropriately concentrated products. Efforts should be made to keep patients on FDA approved products. Patients should be advised of FDA approved

products and encouraged to review their insurance formulary for the best covered option.

Diet Modification for Malabsorption

With adequate PERT patients may not need to restrict the fat content of their diet [10, 37, 95, 97]. A general, healthy diet, would contain about 30% of calories from fat (~65 g fat per day for a 2000 kcal diet) [93], however, the typical American diet may contain far greater amounts of fat. Restriction of fat intake may benefit some patients with severe steatorrhea, Sarner suggests limiting the diet to less than 75 g fat per day [42].

For patients having trouble consuming adequate calories due to limited tolerance of fat, medium-chain triglyceride (MCT) oil may be substituted for other fats because MCTs do not require enzymatic action or bile salts for digestion or absorption [42, 122]. MCT oil is commercially available over the counter, though side effects can include diarrhea, vomiting, nausea, stomach discomfort, and intestinal gas. MCT oil should not be used as a patient's only source of fat as it can lead to essential fatty acid deficiency [42]. Patient compliance may also be an issue as it is not very palatable, however, recipes are available from some manufacturers. Although coconut oil does not provide MCTs exclusively, it is very high in MCTs and may be substituted for other fat sources in the regular diet.

For individuals with malabsorption related to biliary obstruction, symptoms may be reduced by following a low-fat diet until obstruction is corrected [123].

Diarrhea

Diarrhea is common in patients with pancreatic cancer and may be a result of multiple sources including PEI, side effects of chemotherapy or radiation therapy, surgery, or advanced disease. Regardless of etiology, interventions for diarrhea include diet modification (Table 26.3), medications (Table 26.4), and absorptive fiber.

Absorptive Fiber

Patients with diarrhea and/or rapid intestinal transit may benefit from the use of absorptive fiber taken following meals (and at bedtime if indicated). A dose of absorptive fiber is 3.4 g psyllium powder or 1 teaspoon methylcellulose powder blended with 2 ounces water. (May substitute fiber wafers/crisps in place of psyllium powder.) Fiber should be taken after a meal and individuals should avoid drinking fluid for 1 h after. Start once a day and gradually increase as needed up to four times per day (three times a day after meals and at bedtime) [125–127].

Other Considerations

- If metformin is used for DM management, it may contribute to GI side effects including

Table 26.3 Diet and behavior modification for management of diarrhea [24, 124]

Foods to increase
High soluble fiber foods • Banana • Peeled apple, apple sauce (unsweetened) • Oats • Barley
Sodium foods • Salted pretzels or crackers • Broth (room temperature)
Potassium foods • Potato (without skin) • Banana • Coconut water
Foods to minimize
High insoluble fiber foods • Beans, peas, legumes • Whole grains • Fruits and vegetables with thick skins/peels
High sugar foods
Foods that contain sugar alcohol
High-fat and fried foods
Milk products unless low-lactose or lactose-free
Behavior modifications
Maintain adequate hydration • Favor electrolyte containing fluids and oral rehydration solutions • Minimize fluid intake at meals, push fluids between meals • Limit caffeine, alcohol, and carbonated beverages • Avoid hot liquids
Eat smaller meals, more frequently

Table 26.4 Medications to slow intestinal transit [100, 125]

Medication	Common dosing	Maximum dose
Loperamide (Imodium® AD)[a]	4 mg by mouth once then 2 mg after each bowel movement	16 mg/day
	2–4 mg four times a day (every 6 hours)	
Diphenoxylate/atropine (Lomotil®)[a]	1–2 tablets by mouth 3–4 times a day	8 tablets/day
Deodorized tincture of opium	0.3–1 mL by mouth 4 times a day	6 mL/day
Codeine[b]	15–30 mg by mouth three or four times a day	

[a]May be used together, each taken every 6 h, alternating use resulting in individual taking one or the other every 3 h

[b]Used less commonly due to sedation and nausea

diarrhea. Therefore if patients are starting metformin or restarting after a period of the medication being held, gradual dose escalation is advised and possible use of extended-release preparation should be considered [45].

- Diarrhea following, celiac plexus block, may be a transient side effect [100]. Diet strategies may be helpful during the acute recovery following neurolysis.
- For those suspected to have bile acid related diarrhea a bile acid sequestrant (cholestyramine, colestipol) may be prescribed [125].

Special Populations: Perioperative Nutrition, Nutrition at End of Life, Long-Term Survivors

Perioperative Nutrition

Cooper et al. reported on some common themes described by patients regarding post-pancreatic surgery nutrition. Many patients reported struggling with weight loss, being pressured to eat, and feeling they received a lack of appropriate dietary instructions. Patients specified that they wished to have more information regarding what to eat and how often as well as an explanation as to how and why postop diet advice may contradict standard dietary advice (for example, high calorie, high fat diet for rebuilding vs historical beliefs about healthy diet). They also reported needing more information on use of pancreatic enzyme replacement therapy (PERT) and a desire for more information regarding more enduring issues and survivorship [128].

Preoperative Nutrition

Preoperative nutrition intervention is important to reduce risk of surgical complications. Higher rates of surgical site infection, hospital acquired infection, or pancreatic fistula have been reported in patients undernourished before pancreatic resection [129]. In the preoperative setting it is important to manage nutrition related side effects and aid patients in recovery from neoadjuvant treatment, if received.

Preoperative nutrition support is indicated in some cases to improve postoperative outcomes in patients at severe nutrition risk [1]. For these patients at severe nutrition risk, The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends nutrition support for 7–14 days preoperatively, even if causes the operation to be delayed [130]. Jeune et al. recommend enteral feeding for 10–14 days before surgery for those with severe risk for malnutrition [129]. Moreover, it is the consensus of the International Study Group on Pancreatic Surgery (ISGPS) that aggressive preoperative nutrition support is indicated only in severe preoperative malnutrition and should be continued after surgery regardless of early oral intake [131].

Use of immune modulating nutrition (IMN) involves supplementation with novel nutrients such as arginine, omega-3 fatty acids, and nucleotides. IMN use is becoming common in practice [132, 133]. Studies including a Cochrane review meta-analysis conclude that preoperative supplementation with an oral immune modulating nutrition supplement drink for 5–7 days before surgery reduced infectious complications, surgical complications, and hospital length of stay postoperatively in surgical GI cancer patients [38, 132, 134–139]. IMN has been

found beneficial in both well-nourished and malnourished individuals [1, 134].

Postoperative Nutrition

Energy Needs

Sasaki et al. found patients with resectable disease were normometabolic in the preoperative period and needs increased during the postoperative (PD) recovery period. The authors recommend individual daily needs be estimated at 30 kcal/kg/day during postop recovery (6–8 weeks). Alternately the authors recommend a stress factor of 1.2–1.3 if daily needs are calculated using pREE [31].

Early oral feeding, within 24–48 h, following PD is demonstrated to be safe and feasible [1, 140]. It has been associated with decreased length of stay and resulted in no statistically significant differences in complications, DGE, hemorrhage, and mortality when compared to early enteral feeding via NJT [141]. Gerritsen et al. reported findings of a systematic review, concluding there is no evidence to support routine use of nutrition support following PD and oral diet is preferred [141].

Literature suggests that patients may be safely transitioned to a "regular" or "solid" diet over a 3–4 day period [1]. However, what is considered a "regular diet" is generally not outlined and many of these studies take place outside of the USA where the healthcare and food service model may be different. For example, the regular solid food diet outlined by Fujii [142] in the study of postoperative pancreatic fistula (POPF) is considered low-fat (45 g fat per day) in the USA. Therefore, it is the practice of our institution to advance to ice chips, popsicles, and hard candy in the evening the day of surgery, to advance to a clear liquid diet with clear liquid protein supplements on POD 1 or 2, and on POD 3 or 4 to transition to a very low-insoluble fiber, very low-fat, and low-refined carbohydrate (e.g. "low-sugar") diet. At 1–2 weeks following surgery we transition to a less restrictive yet still low-insoluble fiber and low-fat diet. Finally, we return to diet ad lib, 4–8 weeks after surgery, in the absence of enduring side effects or surgical complications. For many patients symptoms may best be managed by avoiding high fat foods long term (such as fried foods, cream sauces, and full fat dairy products) and limiting the diet to 75 g fat per day [42].

Supplementing oral diet with liquid supplement drinks can be helpful to reach calorie, protein, and fluid intake goals during postop recovery [141, 143]. The nutrient composition of these drinks may vary, one study found a supplement drink containing a high proportion of medium chain triglycerides was safe and tolerable in the postoperative setting. [143] Use of IMN oral supplements may provide additional benefit when used perioperatively, see Preoperative and Nutrition Support sections for additional discussion.

Nutrition for Surgical Complications

Nutrition-related side effects of surgery may be transient or result in life-long changes. Some of these symptoms, such as malabsorption and changes in GI transit time, have an effect on an individual's ability to take in and absorb adequate nutrition. Other complications such as chyle leak or pancreatic fistula may be helped with the use of specific nutrition interventions.

Rapid GI Transit or Dumping Syndrome

Rapid GI transit time may occur following pancreatic resection due to dumping syndrome or from denervation during surgery. Though incidence of dumping syndrome is low [78, 144], in those patients who do experience it the symptoms and malabsorption of nutrients can be significant.

Diet modifications for dumping syndrome include avoiding foods containing high amounts of refined sugar (including juice), hot liquids, and any other foods that the individual believes may be causing symptoms. Behavior modifications include avoiding large meals (eat small meals 6–8 times a day) and limit fluid intake with or within 30 min of meals [145, 146].

Pancreatic Fistula

Obesity, malnutrition, and sarcopenia have been identified as individual risk factors for development of postoperative pancreatic fistula (POPF) [147, 148]. Additionally, development of POPF is a risk factor for development of DGE [73, 147].

Because food intake increases the secretion of digestive juices, there is a theoretical concern that food intake will exacerbate POPF however this is not supported by the literature. Fujii et al. demonstrated that in both PD and DP, there were no statistically significant differences in drain output volume, progression to clinically relevant POPF status, or duration of drain placement in those started on oral diet (maximum of 45 g fat per day) on postoperative day 5 versus those on only parenteral nutrition and nothing by mouth [142, 149]. Nahm et al. suggest resumption of oral diet as usual in patients with PJ or no anastomosis (ex. distal pancreatectomy) and in pancreaticogastrostomy to first rule out a mechanical anastomotic leak before resuming oral diet [147]. Though oral diet should be the primary approach, if patients require nutrition support, enteral nutrition is superior to parenteral nutrition. In a study of enteral versus parenteral nutrition there were greater rates of spontaneous fistula closure in the enterally fed group [150].

Chyle Leak

Nutrition interventions suggested for patients with chyle leak vary widely and include "fat-free" diet; low-fat diet; diet supplemented with medium-chain triglycerides; low-fat, high MCT enteral nutrition (EN) formula; NPO or clear liquid diet with parenteral nutrition (PN); or a combination thereof [151, 152]. There is a paucity of data to conclude superiority of one intervention over another [153]. Generally, it is ideal that patients be maintained on oral diet, if not then EN is preferred over PN. There is a risk of essential fatty acid deficiency in patients on a minimal fat diet for more than 3 weeks [154]. Lipids administered via IV will not contribute to chyle volume—they may be used as part of PN or administered three times per week to avoid essential fatty acid deficiency in a patient otherwise maintained on a fat-free/minimum fat diet. A fat-free diet is generally acknowledged as limiting intake to only those foods with less than 0.5 g fat per serving. Sriram et al. recommend that patients be maintained on the intervention of choice for 7–10 days and that diet be advanced as chyle drainage volume decreases [151].

Nutrition Support

Indications for nutrition support have been discussed throughout the chapter. Nutrition support can be in the form of either enteral nutrition (EN) or parenteral nutrition (PN). EN is preferred over PN due its beneficial effects on the digestive system, and reduced risk for infection as compared to PN [130, 131, 155–157]. EN helps maintain the natural way of nutrient absorption, helps maintain intestinal mucosa, bile salt management, and secretion of gastrin. It stimulates peristalsis and therefore may reduce the presence of pathogenic bacteria in the intestinal lumen. EN also stimulates intestinal blood flow and supports immune system by decreasing inflammatory processes within the GI tract [158].

PN for surgical patients should only be utilized when a patient cannot be fed via their digestive tract, such as cases of ileus, GI obstruction, severe shock, intestinal ischemia, and high output fistulas [130, 158]. It is important to note that PN typically requires hospital admission due need for central line placement and monitoring of daily labs due to fluctuations in blood glucose, electrolyte disturbances, and potential refeeding syndrome. A study by Worsh et al. evaluating the use of PN following surgery found that patients who developed DGE may be overprescribed PN, but patients with DGE accompanied by another postoperative complication such as surgical site infection or POPF were more likely to require PN >3 days [159]. Thus, PN is a useful tool, but should not be overused.

The use of nutrition support in the postoperative setting continues to be debated, and much of the use of nutrition support is left to individual surgeon preference. Early postoperative oral feeding is considered the preferred mode of nutrition for surgical patients, according to ESPEN guidelines [130]. At this time there is not suffi-

cient evidence to support either enteral or parenteral feeding over oral feeding, and oral diet should be first choice, although nutrition support is indicated in aforementioned instances [130]. The ISGPS states that it is reasonable to place a feeding tube at the time of PD if the patient is severely malnourished, at high risk for pancreatic fistula, or in cases of reoperation for abdominal complications [131]. However, in the postoperative setting there are concerns that placement of a feeding tube itself is associated complications that can cause a delay in resuming oral intake. Tube-specific complications that are reported to occur in 5–20% of patients include: site infection, pneumatosis intestinalis, diarrhea, and tube malfunction [38, 160]. Use of naso-jejual tubes (NJT) seem to show no difference in complications, infections, or length of stay over directly placed feeding tube, and been reported to dislodge in up to 36% of cases [131, 161]. A retrospective analysis of 4390 patients who underwent feeding jejunostomy tube placement at the time of PD suggested that feeding j-tube placement may be associated with increased postop complications, specifically infection, pneumonia, acute renal failure, and sepsis, however, it should be noted that there were a multitude of differences between the two study groups [162].

Some recent literature compared postoperative EN with a combination of EN and PN in patients after PD in single centers. In a small study (n = 36), Jiang and colleagues compared patients who received 3 days of PN then transitioned to EN, versus EN alone and found the only significant change in outcomes to be decreased postop weight loss [163]. In another single center study of PD patients, Lu and colleagues found that a combination of early enteral nutrition supplemented with PN resulted in increased incidence of DGE and pneumonia than TPN alone [164].

Special consideration should be given to EN formulas for pancreatic cancer patients with PEI. For those patients, it is ideal to use a semi-elemental, high medium chain triglyceride formula to limit the need for supplemental pancreatic enzymes during tube feeding [165, 166]. For patients with severe PEI or where semi-elemental formula produces a financial burden to the patient, administration of PERT with EN may still be necessary. When administering pancreatic enzymes with enteral feeding, enzymes should be administered about every 3 hours during continuous or cyclic feedings. For intermittent feedings via gravity or bolus feeding, enzymes may be delivered with each feeding. Ferrie et al. outline appropriate methods of enzyme delivery via feeding tube—if the patient has a large bore gastrostomy tube the enzyme microspheres may be delivered in a thickened liquid, if the tube is small bore or a j-tube enzymes should be crushed and/or dissolved with bicarbonate prior to administration through the tube [166]. Enzymes may also be taken by mouth in tandem with enteral feeds [167]. Though data is limited at this time, studies in humans with cystic fibrosis demonstrate that fat absorption from EN is enhanced with the use of an in-line digestive cartridge (Relizorb®) that possibly takes the place of pancreatic enzyme capsules for these patients [168, 169]. These findings suggest potential benefit of this cartridge for individuals with other etiologies of PEI.

A recent study by Miyauchi and colleagues investigated the use of preoperative versus perioperative IMN in PD patients. Researchers compared patients who received IMN orally preoperatively versus patients who received IMN both preoperatively and postoperatively (via J tube postoperatively) but found no difference in outcomes between the two groups [133]. This may suggest that while preoperative IMN is beneficial, perioperative IMN does not demonstrate additional benefit at this time for this population. While results are mixed, some literature does suggest that if EN is used postoperatively, an IMN formula may reduce the risk of postop complications, infections, and be associated with shorter length of stay [38].

End of Life

Once a patient enters the refractory cachexia stage, the focus of interventions should shift to palliation and symptom control, as these take priority over curative strategies [7, 13]. In this stage,

risks and encumbrance of artificial nutrition support tend to outweigh potential value, since ultimately these efforts have not been shown to reverse cachexia [7, 13]. PN should not be prescribed near the end of life, considering ESPEN guidelines PN should be considered only if GI tract is not functional AND in the absence of heavy metastatic dz burden, and if vital prognosis is conditioned by nutritional status rather than disease [1]

Ascites

Presence of ascites within 2 months of diagnosis of PC is reported in about 1/5 of patients [170]. Others may develop ascites as part of late-stage disease [170]. Poor appetite and early satiety may accompany ascites. Diet strategies for delayed gastric emptying (discussed elsewhere in this chapter) may be helpful for coping with early satiety related to ascites. There is no evidence regarding sodium restriction in cancer associated ascites; however, it is suggested in practice [171] and is found beneficial in ascites that has a high (≥1.1 g/dL) serum-ascites albumin gradient (SAAG) [172–174]. If patients are not already self-limiting sodium due to decreased food volume intake and SAAG is known, it is reasonable to consider a no added salt (~2 g sodium) diet for those with high SAAG.

Long-Term Survivors

Because of the limited long-term survival of PC, studies of long-term survivors are limited. Therefore, nutrition recommendations are largely based on small populations and case studies of patients with nutritional deficiencies. Incidence of specific nutrient deficiencies in this population remain unknown. Given the surgical history for treatment of PC, along with malabsorption that may occur due the cancer itself, these patients are at increased risk for vitamin and mineral deficiencies (Table 26.5). Specifically, deficiency may be due to inadequate food intake, loss of absorptive site, and alterations in physiology, synchrony and chemistry of the GI tract [115]. It is recommended that patients be evaluated for micronutrient deficiency (Table 26.5) within 1 year after surgical resection or sooner if patient has signs or symptoms of malabsorption or nutrient deficiency. For those with normal serum results, reevaluation is recommended annually. For deficiency, repletion (Table 26.5) should be attempted and serum levels should be rechecked about 3 months later [115].

Nonalcoholic fatty liver disease (NAFLD) or hepatic steatosis is reported to occur in 7–40% of patients following pancreatectomy [115]. The exact etiology is unknown but potential causes include the malabsorption of amino acids, fat-soluble nutrients, and fatty acids. Such malabsorption is thought to lead to accumulation of triglycerides in the liver. PERT has been suggested and is being studied as a possible treatment for NAFLD in the post PD/PPPD patient due to its mechanism for preventing fat malabsorption. At this time the studies are compelling and suggest an importance of adequate control of PEI in these patients even in the absence of clinical symptoms [115].

There is concern that long-term post PD patients may be at an increased risk for bone density loss due to removal of the duodenum, the primary absorption site of calcium. These patients are also routinely on acid-suppressive therapy which changes the solubility of calcium. Studies evaluating patients with pancreatic insufficiency, total pancreatectomy, and Roux-en-Y gastric bypass found an increased risk of osteopenia or osteoporosis in these groups, suggesting that surgery and malabsorption both my play a part in reduced bone density [93, 115]. Although there is not copious supporting literature, the existing literature suggests it is important to monitor bone density in long-term PC survivors. Practice-based recommendations suggest obtaining baseline bone mineral density exam after completion of surgical recovery and any adjuvant treatment, within 2 years after surgery. If results are normal recheck every 5 years, if abnormal refer to primary care team or bone health specialist for care [115]. Recommendations for bone health should include ensuring adequate calcium intake via diet

Table 26.5 Recommendations for micronutrient evaluation replacement and maintenance [115]

Micronutrient	Bloodwork to evaluate	Rebuild	Maintain	Trouble shooting
Vitamin A [175]	Vitamin A	30,000 IU retinol palmitate, 1 daily p.o. for 4 weeks	DRI	Parenteral administration may be necessary if unable to normalize serum
Vitamin B6 [176]	Vitamin B6 (pyridoxal 5-phosphate (PLP) and pyridoxic acid)	60 mg pyridoxine daily for 3 weeks	DRI	–
Vitamin B12 [177]	CBC Vitamin B12 Methylmalonic acid	1000 mcg cyanocobalamin, intramuscular injection once a month	1000 mcg cyanocobalamin intramuscularly once a month or 1000 mcg vitamin B12, 1 daily p.o.	If unable to maintain with oral dosage change to monthly intramuscular injection
Vitamin D [178]	25-OH vitamin D	50,000 IU of cholecalciferol or ergocalciferol, p.o., once a week for 8 weeks	1500–2000 IU cholecalciferol, 1 daily p.o. or 50,000 IU cholecalcifereol or ergocalcierol, p.o. once every other week	Patients who are obese or have malabsorption may require 2–3 times the stated dose (see next section)
		6000 IU of cholecalciferol or ergocalciferol once a day for 8 weeks	1500–2000 IU cholecalciferol, p.o. once a day	Patients who are obese or have malabsorption may require 2–3 times the stated dose (see next section)
Vitamin D Obese or malabsorbing [175, 179]		50,000 IU of cholecalciferol or ergocalciferol, p.o., 3 times a week for 4–8 weeks	3000–6000 IU cholecalciferol, p.o. once a day	–
		6000–20,000 IU cholecalciferol or ergocalciferol, p.o., once a day for 8 weeks		
Vitamin E [175]	Alpha tocopherol	400 IU p.o. once a day for 2 weeks	DRI	–
Copper [179]	Copper Ceruloplasmin	3–8 mg elemental copper, p.o. per day, until levels normalize	DRI	Ensure patient not taking excessive amounts of zinc
Iron [115, 180]	CBC Ferritin Total iron binding capacity Iron	150–200 elemental iron daily or every other day, p.o. in 2 or 3 divided doses	DRI	Intravenous administration may be necessary if unable to normalize serum
Selenium [179]	Selenium	100 mcg selenium p.o. once a day, until levels normalize	DRI	–
Zinc [179, 181]	Zinc	50–60 mg elemental zinc, p.o., 1–2 times a per day for 3 months	DRI	–

DRI dietary reference intake
p.o. by mouth

or supplements, monitoring for adequate serum 25-OH vitamin D, and including frequent weight-bearing activities.

Summary

Whether patients have resectable or advanced disease, medical nutrition therapy can improve treatment outcomes and empower patients and families to play an active role in their care for pancreatic cancers. For those patients who survive long term, the nutrition implications of the disease and treatments are likely to endure for the rest of their lives and continued nutrition intervention may be necessary. It is important to help patients cope with nutrition issues throughout the course of treatment and disease.

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27 Prioritizing the Patient Experience: Early Integration of Supportive/Palliative Care in Pancreatic Cancer Management

Ishwaria M. Subbiah and Lillian Wieland

Introduction

Palliative care is a multidisciplinary subspecialty dedicated to the overall quality of life of the patient as well as their families when facing life-limiting illnesses. Indeed, the World Health Organization (WHO) defines this field as an approach dedicated to "the relief of suffering by means of early identification an implantable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. The WHO further characterizes the domains of palliative care as they apply not just to the patient but also those closest to them including families and informal caregivers (Table 27.1). Across the world annually, approximately 40 million people are in need of the services of palliative care but, however, among those needing palliative care at the end-of-life, at this time only approximately 14% receive it [2]. While timely and broader access to palliative care remains a target for health systems within the USA and worldwide, the body of literature to support the role of palliative care in patient centered outcomes continues to build. The morbidity and mortality of pancreatic cancer has been well characterized with an estimated 57,600 adults in the USA alone expected to be diagnosed in the year 2020 and an estimated 47,050 deaths from pancreatic cancer within that same 1-year period [3]. The impact of pancreatic cancer on individual patient-family units as well as the broader community inherently calls for the early integration of palliative care.

Table 27.1 The World Health Organization Definition of Palliative Care in Cancer

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 aid to families for coping during the illness and bereavement
Uses a team approach to address the needs of patients and their families
Aims to enhance quality of life and positively influence the course of illness
Is applicable early in the course of illness
Collaborates with therapies intended to prolong life such as chemotherapy or radiation
Includes tests needed to better understand and manage distressing clinical complications

Adapted from https://www.who.int/cancer/palliative/definition/en/

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_27

Early Integrated Palliative Care in Patients with Cancer

Several studies demonstrate the impact on patient reported outcomes when palliative care is integrated early into pristine cancer care. One such randomized controlled trial enrolled patients within 8 weeks of a new diagnosis of the metastatic lung (including small cell, non-small cell lung cancer or mesothelioma) or non-colorectal gastrointestinal cancer cancers of pancreatic, esophageal, gastric, or hepatobiliary in origin [4]. Patients were randomized to receive early integrated palliative care with oncologic care versus usual oncologic care. In the intervention arm, patients had an encounter with the outpatient palliative care team within 4 weeks upon randomization to the early palliative care arm as well as at least once a month until their death with additional visits at the discretion of the palliative care clinicians. The quality of life was measured using the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) scale, which assesses the physical, functional, emotional, and social well-being dimensions of quality of life [5]. Additional measures for mood, anxiety, and depression included the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale (HADS) [6, 7]. The study also measured the prognostic understanding of the patient as well as their perception of communication with their oncology teams using the Prognosis and Treatment Perceptions Questionnaire [8]. Overall, 350 patients participated on this trial with the median age of approximately 65 years in both the usual care arm as well as the early palliative care arm. At the 24-week mark, patients in the palliative care arm had an average of 6.54 visits with the palliative care team versus 0.89 visits in the usual care group. For the statistical mottling demonstrated that patients in the intervention arm had a significantly higher quality of life on the FACT-G and lower symptoms of depression on the PHQ-9 at 2 and 4 months; however, this change did not persist at the 6-month mark before death (Table 27.2).

Regarding prognostic understanding and communication, patients in the early palliative care arm were more likely to report that knowing about their prognosis was "very helpful" or "extremely helpful" in treatment decision making (96.5% [n = 110 of 114] v 89.8% [n = 115 of 128]; P = 0.043) and coping (97.3% [n = 108 of 111) v 83.6% [n = 107 of 128]; P < 0.001) at 12 weeks. Furthermore, when compared to the usual care arm, a significantly greater proportion of patients in the intervention early palliative care arm (30.2% [n = 35 of 116] v 14.5% [n = 17 of 117]; P = 0.004) reported having discussions with their oncologist regarding their end-of-life wishes, at the 24-week mark.

The second cluster randomized control trial of 461 patients with advanced cancer assessed the impact of early palliative care referral and follow-up in combination with oncologic care versus standard cancer care on measures of quality of life [9]. This study employed the following measures at baseline and at monthly intervals for total 4 months: Quality of life (measured using the Functional Assessment of Chronic Illness Therapy--Spiritual Well-Being [FACIT-Sp] scale and Quality of Life at the End of Life [QUAL-E] scale), symptom severity (Edmonton Symptom Assessment System [ESAS]), satisfaction with care (FAMCARE-P16), and problems with medical interactions (Cancer Rehabilitation Evaluation System Medical Interaction Subscale [CARES-MIS]) [10–14]. The change in the FACIT-Sp score at the 3-month mark was defined as the primary outcome with the secondary outcomes being change in the FACIT-Sp at 4 months and change in the QUAL-E, ESAS, FAMCARE-P16, and CARES-MIS at the 3- and 4-month mark. Interestingly, the study findings report the changes at the 3-month mark to be nonsignificant between the usual care arm and the intervention arm. However, at the 4-month mark, this changes within the FACIT-Sp, QUAL-E, ESAS, and FAMCARE-P16 were all statistically significant and in favor of the early palliative care arm with the FACIT-Sp score change of +2.46 [15 - 47] vs −3.95 [14 - 21], p = 0·006, QUAL-E (+3.04 [8 - 33] vs −0.51 [7 - 62], p = 0·003), and ESAS

Table 27.2 Characterization of components of a multidisciplinary palliative care team in comparison with traditional oncologic care

	Palliative care	Standard care
Outpatient clinics		
Staff	Clinical team including physician, advanced practice providers, and nurse with specialist training in palliative care	Oncologist, advanced practice providers, and oncology nurses with likely limited to no formal palliative care training
Visits	At least once a month with additional visits as clinically indicated	Variable frequency of visits often driven by chemotherapy cycle timings
Symptom assessment in clinic	Routine, structured assessment every visit by palliative care nurse and physician	No nationally standardized structured assessment
Psychosocial assessment in clinic	Routine assessment of patient and family support needs, of patient and family coping and psychological distress; discussion of advance care planning guided by patient and family readiness	No nationally standardized routine structured assessment
Telephone follow-up	Routine calls made by palliative care nurse scheduled at a frequency determined by clinical need and symptom burden by the palliative care clinician	As needed by oncology nurse or advanced practice provider with access to oncologist
On-call service	24-h on-call service explained during first visit; provided by specialized palliative care physicians	Access to 24-h on-call service (oncology resident or clinical associate)
Hospital service		
Inpatient care	Direct admission to palliative care unit for symptom management	Admission to oncology ward or medical ward (via emergency center)
Inpatient staff	Specialty-trained physicians and advanced practice providers	Primary services in general oncology or general medicine
Palliative care inpatient consultation team	Follow-up by palliative care team when admitted to non-palliative-care-unit service	No routine follow-up by palliative care team unless specifically engaged by primary services
Home-based care		
Multidisciplinary home services (e.g. physical and occupational therapy, etc.)	Explained and offered during first visit; reassessed at each visit	Ad hoc
Communication with primary care physician	Routine with chronic advanced illnesses, as needed in the context of advanced cancer care	Rarely in the context of advanced cancer care
Approach to care		
All care providers	Multidisciplinary, addressing physical, psychological, social and spiritual needs	Ad hoc, mainly addressing physical needs

Adapted from Zimmerman C, et al. Early palliative care for patients with advanced cancer: a cluster-randomized controlled trial. Lancet. 2014 May 17;383(9930):1721–30

(−1.34 [15 - 98] vs +3.23 [13 - 93], $p = 0{\cdot}05$). These and other studies demonstrate compelling findings that emphasized the impact of early integration of palliative care on multiple dimensions of quality of life, satisfaction with care, and other critical elements of the oncology treatment experience.

Toxicities and Healthcare-Related Quality of Life Outcomes of Systemic Therapy

The morbidity inherent to diagnosis of pancreatic cancer particularly in the context of high risk for recurrence or unresectable/advanced disease at

the time of diagnosis calls for multidisciplinary, comprehensive, whole person symptom management in conjunction with cancer directed treatment. For patients receiving systemic therapy in the unresectable or metastatic disease setting, the toxicities related to disease directed therapy whether it is combination chemotherapy or radiation can be considerable. One study examine the impact of 5-flourouacil, irinotecan, and oxaliplatin (FOLFIRINOX) when compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer [15]. The authors conducted an analysis of the results from the PRODIGE 4/ACCORD 11 randomized trial which enrolled 342 patients with an ECOG performance status of 0 or 1 to be randomized to receive FOLFIRINOX or gemcitabine as first-line chemotherapy. They assessed quality of life using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) completed by the participants every 2 weeks [16]. Furthermore, they assessed whether the baseline quality of life prior to the start of treatment was predictive of survival in this specific patient population. Overall, they reported an improvement in the emotional functioning ($P < 0.001$), pain, insomnia, and anorexia in both the FOLFIRINOX and gemcitabine arms as well as an improvement in the global health status in the FOLFIRINOX arm. As expected, patients receiving FOLFIRINOX reported a significantly higher incidence of diarrhea then dose receiving gemcitabine in the first 2 months of systemic therapy. Furthermore, when directly compared with gemcitabine, those patients receiving FOLFIRINOX had a significantly longer time until deterioration of their quality of life domains (global health status, physical, role, cognitive, and social functioning, and six symptom domains [fatigue, nausea and vomiting, pain, dyspnea, anorexia, and constipation]). Indeed, while the patients receiving FOLFIRINOX demonstrated a significantly improved objective response rate (31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group, $P < 0.001$), they also reported higher incidence of adverse events [17]. Specific grade 3 or 4 nonhematologic symptom related toxicities were significantly higher in the FOLFIRINOX group such as diarrhea (12.7% in FOLFIRINOX vs. 1.8% in gemcitabine, $P < 0.001$) and sensory neuropathy (9.0% in FOLFIRINOX vs. none reported in gemcitabine, $P < 0.001$). When analyzing the global measures of quality life at the 6-month time point, 31% of the patients in the FOLFIRINOX group demonstrated a definitive degradation of the quality of life while 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; $P < 0.001$). The findings of the studies centered around the high burden of symptoms were echoed in others evaluating systemic therapies for patients with metastatic pancreatic cancer [18].

Similarly, in the phase 3 randomized control trial of patients with metastatic pancreatic cancer, treated in 61 patients were randomized to receive either gemcitabine alone or gemcitabine plus nab-paclitaxel [19]. The study did demonstrate an improvement in median overall survival as well as 1- and 2-year survival rates favoring the combination arm. However, closer examination of this statistically significant improvement of 1.8 Months highlights the significant mortality associated with this disease (median overall survival 8.5 months in the nab-paclitaxel–gemcitabine group versus 6.7 months in the gemcitabine group; hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; $P < 0.001$). The most common high grade non-hematologic toxicities included fatigue and neuropathy with rates significantly higher in the combination arm (fatigue 17% vs. 7%, neuropathy 17% vs. 1%). Overall, a similar proportion of patients in both groups reported serious adverse events (50% in nab-paclitaxel plus gemcitabine cohort and 43% in gemcitabine alone).

When examining toxicities in the context of multimodal therapy such as radiation in addition to chemotherapy, one Eastern Cooperative Oncology Group trial randomized patients with locally advanced pancreatic cancer to receive gemcitabine alone versus gemcitabine plus radiotherapy [20]. Overall, this study of 74 patients with locally unresectable pancreatic adenocarcinoma demonstrated an improved overall survival

in the cohort receiving the combination of gemcitabine with radiation versus radiation alone. Furthermore, the majority of patients in both arms experienced grade 3 and 4 toxicities with the rate being comparable in both arms (77% in gemcitabine alone versus 79% in gemcitabine plus radiation, $P = 1.0$). Quality of life measurements were obtained using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, which includes 27 items to assess physical, functional, emotional, and social well-being and 18 items to assess hepatobiliary-specific concerns [21]. The FACT-Hep did not demonstrate any statistical significance in both arms at multiple time points (baseline, and 6, 15 or 16, and 36 weeks on study, even if the patient is discontinued therapy). However, more strikingly, the analysis demonstrated that participants in both arms experienced a statistically significant decline in health care related quality of life from baseline to week 6, highlighting the morbidity associated with the systemic therapies as a whole for this particular type of cancer.

Integration of Health Care Related Quality of Life Measures into Clinical Trials

Advances in cancer therapies overall have translated to a lesser extent for patients with metastatic pancreatic adenocarcinoma where survival rate remains low and the proportion of patients who present with unresectable of metastatic disease remains consistently high over the past several decades [22]. Indeed, the combination of disease related symptoms particularly with progression of cancer as well as the toxicities related to the cancer directed therapy produce a high burden of global symptoms [23, 24]. Consequently, the management of symptoms and their associated impact on quality of life intuitively take significant priority in the care of these patients. Indeed, in the area of sound clinical trial design, an increasing number of studies integrating patients with metastatic pancreatic cancer have integrated formal, independently validated measurements of health related and other quality of life related outcomes [25, 26].

Indeed, early trials of gemcitabine demonstrated an improvement in disease related symptoms-these findings ultimately prompted the definitive trial establishing its role in the management of patients with newly diagnosed advanced pancreatic cancer. The randomized control trial of 126 patient's receiving either gemcitabine or 5-fluorouracil had the primary efficacy measure designated as a clinical benefit response, which was a sustained improvement lasting 4 weeks or more in the composite measure of pain (analgesic use and pain intensity), Karnofsky performance status, and weight [27]. In fact, in this study, the more widely known and measures of efficacy such as response rates, time to disease progression, and overall survival were needed as secondary outcomes. Indeed, the study demonstrated alleviation of disease-related symptoms that are higher rate with gemcitabine versus 5-FU with a modest increase in overall survival.

Similarly, the practice changing study of FOLFIRINOX versus gemcitabine for patients with previously untreated advanced pancreatic cancer integrated quality of life as a secondary and point [17]. To add, the findings from the quality of life component of this study provided critical information on the delay in deterioration in quality of life seen with FOLFIRINOX, a finding that carries particular value for frontline clinical decision making. However, standardization of quality of life measures into clinical trials with pancreatic cancer remains a target. The seminal study for nab-paclitaxel in combination with gemcitabine versus gemcitabine alone did not assess quality of life using rigorous validated instruments, instead reporting on the traditional toxicities alone [19].

Providing Holistic Care for Patients with Pancreatic Cancer

The approach to symptom management whether it is in the context of clinical trial design or patient care begins with the recognition of the

whole-person impact of cancer. The intuitive attention paid to common physical symptoms such as pain, nausea, or shortness of breath are understandable given that these are among the more perceptible signs and symptoms. However, recognition of the psychosocial, functional, financial, social domains among others concurrently with physical symptoms and objective measures of disease status form the cornerstone of holistic care. Existing tools and symptom scale questionnaires generally integrate multiple domains of well-being and symptoms that extend beyond the more traditionally employed functional status assessments such as the Eastern Cooperative Oncology Group Performance Status (ECOG PS) or Karnofsky performance status scores [28, 29]. Given the variability in the definitions of quality of life, these scales provide a more systematic and structured approach to symptom assessment that are driven by the patient's own report of their symptom burden, i.e. patient reported outcomes (PROs). These instruments serve as a validated measure of symptom burden and individual instruments provide insight into different domains of a patient's well-being (Table 27.3). While all are relevant to the patients with pancreatic cancer, instruments such as the FACT-HEP and FACT-Hepatobiliary Symptom

Table 27.3 Health-related quality-of-life scales in use for patients with pancreatic cancer

Scale	Description
EORTC QLQ—C30	HRQoL questionnaire; 30-item scale with 28 questions related to function: Namely physical, role, cognitive, emotional, and social and three symptom scales: Fatigue, pain, and nausea and vomiting with a 4-point response scale. A further two questions assess overall ratings of health on a 7-point response scale. 4-point response scales common across EORTC questionnaires: not at all, a little, quite a bit, very much
EORTC QLQ-Pan-26	26-item scale with questions regarding pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, and taste changes). Currently undergoing validation in clinical trials
EORTC QLQ-C15-PAL	15-item scale for patients undergoing palliative care. 14 questions around mood, bowel habit, energy levels and oral intake on a 4-point response scale and 1 question about overall health on a 7-point response scale
Functional assessment of cancer therapy—general; FACT-G	28-item scale with sections for physical, emotional, functional, and social Well-being on a 5-point response scale
FACT-HEP	Hepatobiliary (including pancreas) cancer-specific scale consisting of the 28 items in FACT-G, with a further 18-items on a 5-point response scale, with questions regarding specific symptoms including jaundice, abdominal pain, and changes to bowel habit
FACT-hepatobiliary symptom index—FHSI	Shorter 8—Item hepatobiliary cancer-specific scale with questions regarding jaundice, abdominal discomfort, back pain, weight loss, change to bowel habit, nausea and lethargy
Hospital anxiety and depression scale—HADS	14-item scale with 7 items each for questions relating to anxiety and depression symptoms on a 4-point response scale. Total potential score of 21 for anxiety and depression respectively and a score of 8 or more routinely taken as representing significant symptoms
Patient-health questionnaire—9 PHQ9	9-item scale used as a screening tool for depression with questions relating to anhedonia on a 4-point response scale
Euro-QoL 5 dimensions questionnaire—EQ-5D	6-item scale consisting of five questions related to physical function and symptoms on a 3-point response scale and a visual-analog rating of overall health from 0 to 100
Edmonton symptom assessment scale (ESAS)	8-item scale consisting of visual-analog assessments of pain, activity levels, nausea, drowsiness, depression, anxiety, appetite and sense of Well-being on a 0–100 scale. Designed to be repeated daily and variation assessed

Adapted from Lewis AR, et al. The importance of quality-of-life management in patients with advanced pancreatic ductal adenocarcinoma. Curr Probl Cancer. Jan-Feb 2018;42(1):26–39

Index (FHSI) were developed as when necessary measures specific for hepatobiliary cancers including pancreatic cancer and in addition to the core symptom items, both include questions on symptoms common to hepatobiliary cancers such as jaundice, change in bowel habits, abdominal pain [30]. These and other instruments can serve as critical components of tailored symptom assessments for patients with pancreatic cancer.

Underutilization of Palliative Care in Cancer Therapy and Barriers to Earlier Integration of Palliative Care

Despite early referral to palliative care being emphasized in consensus guidelines from multiple oncologic bodies, barriers to earlier integration and referral remain widely prevalent. Accessibility to multidisciplinary subspecialties symptom management teams may be limited geographically, a disparity most evident in low- and middle-income countries [31]. Other themes centered around access to palliative care often highlight biases and misconceptions within both the clinical community as well as the patients and families, a common one being palliative care as service only to be accessed at the very end-of-life. Indeed, in a cluster randomized controlled trial of early palliative care versus standard care for patients with advanced cancer, the investigators conducted semi-structured qualitative interviews to assess patient and caregiver attitudes and perceptions about palliative care [32]. The findings from their interviews at 48 patients and 23 caregivers revealed the participants initial perceptions of palliative care to be associated with death, hopelessness, dependency, and comfort care at the end of life. Interestingly, patients who participated in the interviews who were randomized to the early palliative care arm of that trial unequivocally emphasize the importance of an alternate name for the palliative care service in the outpatient setting particularly if early integration is considered a goal.

To conclude, multiple studies have characterized the impact of early integration of subspecialty palliative care services for patients with advanced cancer. This impact extends to domains related to quality of life, satisfaction with care, as well as individual symptoms including pain and depression. For patients with pancreatic cancer, the management approach in any setting, be curative intent or metastatic disease, brings considerable morbidity and mortality, which are not just treatment related but also as a consequence of the disease itself. In this context, integration of a dedicated subspecialty palliative care team beginning at the time of diagnosis can effectively complement the disease directed treatments to ensure goal concordant care.

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Patient Reported Outcomes and Quality of Life

28

Connor P. Thunshelle, Eugene J. Koay, Colin Hill, Catherine M. Alfano, and Joseph M. Herman

Introduction

Pancreatic cancer is known to be one of the most aggressive malignancies, with a cumulative 5-year overall survival (OS) of around 9% [1]. Moreover, the incidence and mortality of pancreatic cancer is expected to increase in coming years and pancreatic cancer will become the second most common cause of cancer death in the USA in 2040 [2]. Most cancer trials focus primarily on an OS endpoint to determine the true efficacy of a specific intervention, be it for systemic or local therapeutic modalities. Given the diversity of patient presentations with pancreatic ductal adenocarcinoma (PDAC), primarily focusing on an OS benefit may fail to capture other benefits that therapies may provide—such as quality of life (QoL) and symptom improvement, which would be meaningful in patients who present with a poor performance status (PS) and advanced disease that carries a limited chance of a cure [3]. While extending OS should be a primary focus of any intervention, it is imperative to maximize QoL and minimize treatment-related toxicity and cancer-related symptoms. The experience of patients with PDAC should not be understated as they often experience substantial disease related morbidity that is compounded by treatment-related toxicity especially in elderly patients or those with advanced disease. To date, the benefits of any therapy on OS for PDAC have been comparatively modest. Given the overall poor prognosis for patients with PDAC and the fact that mortality is not expected to significantly improve in the near future, treatments that can improve QoL or symptom burden will be especially meaningful in this patient population.

Even with the improvements in the side effect profile of aggressive systemic therapeutic regimens and technological advancements with local

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_28

therapeutic modalities, QoL outcomes for PDAC remain unacceptably low. A population-matched analysis of PDAC patients with an age-matched healthy patient cohort demonstrated a 98% loss of healthy life and a loss of 610,000–915,000 quality-adjusted life-years (QALYs) annually [4]. PDAC patients also had significantly lower scores on validated health-related quality of life instruments versus population norms [5].

Precedence for the use of QoL metrics has been established for investigating the benefit of various therapeutic modalities such as surgery, systemic therapy, and radiation for pancreatic cancer. For example, a randomized trial in the 1990s used a composite endpoint, termed "clinical benefit" of pain, Karnofsky performance status (KPS) after treatment, and weight to investigate the efficacy of gemcitabine in patients with advanced stage PDAC [6]. Although there was a significant but only modest median OS benefit with gemcitabine, the "clinical benefit" with gemcitabine was 23.8% versus only 4.8% with 5-fluorouracil chemotherapy [6]. However, these metrics remain largely underutilized in PDAC and significant heterogeneity remains in how they are used to capture the patient experience and define the benefit of various therapeutic modalities [7].

Going forward, increased emphasis should be placed in future studies and trials on metrics that can accurately capture the patient experience and define the QoL benefit when evaluating new therapies and interventions for pancreatic cancer.

Definitions of Quality of Life

Historically, physician-graded measures, such as performance status (PS), have been used to measure a patient's QoL in the form of disease burden [8]. The most common metrics used to define PS in PDAC include Karnofsky Performance Status (KPS) and the scoring system described by the European Cancer Oncology Group (ECOG) [4, 9]. KPS describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death) [4]. The ECOG system was derived from KPS and utilizes a simpler scoring system from 0 to 5 with zero being in excellent health and five signifying death [4]. Although PS scores can be prognostic for survival and provide a consistent way to determine if a patient will be eligible for various therapeutic modalities, they often lack the granularity to drive specific treatment decisions [8]. Nevertheless, most clinical trials include ECOG or KPS as part of the inclusion criteria. Moreover, PS scores like other physician-graded measures, such as the Common Terminology Criteria for Adverse Events (CTCAE) criteria, are subjective and determined by healthcare providers as opposed to being self-reported by the patient. For example, in a multidisciplinary setting it is not uncommon for multiple providers to give different ratings of performance status and Common Terminology Criteria for Adverse Events (CTCAE) criteria for the same patient. This could be addressed by having all data points collected in aggregate, ideally in a dashboard within an electronic health record. This way decisions can be made when there are discrepancies, however, there may still be some incongruence between physician-graded measures and patient reported assessments. In addition, physician-graded measures may not fully capture the range of patient concerns with treatment and disease burden such as maintaining sexual intimacy [7].

Conversely, healthcare related quality of life (HrQoL) assessments are completed by patients, caregivers, and/or with the assistance of the healthcare team. HrQoL evaluations are structured assessments that use data provided by patients and/or family members but are processed with a specific methodology to produce a score or measure that can be used to assess a patient's baseline status or evaluate how a specific treatment regimen alters their current state (positively or negatively). It may cover direct experience of disease or treatment but will also include specific questions which are important to the condition experienced by the patients. The general or global component often includes physical, social, or psychological parameters. The broader term Quality of Life (QoL) will also include factors beyond healthcare and will try to include all aspects of a patient's life. Historically, when QoL was included as part of a clinical trial, HrQoL evaluations were often done on paper and stored away until the completion of the clinical trial. The responses from these HrQoL questionnaires

were not usually incorporated into the routine management of patient care and therefore did not address the acute needs that patients may have.

Patient reported outcomes (PROs) are reports of a patient's status on a specific issue or health condition that comes directly from the patient, without interpretation by a clinician or anyone else [10]. Patient Reported Outcome Measures (PROMs) describe how a patient functions or feels in regard to a condition or therapy, and includes a variety of constructs and methodologies. PROMs can encompass concepts from specific physical symptoms to overall physical function, well-being, and social involvement. HrQoL assessments are a type of PROM that are multi-dimensional, focusing on the patient's overall perception of the effect of their illness and treatment. PROMs can provide an assessment of symptom burden during treatment and are often utilized to provide real-time supportive care and or change management such as adjusting chemotherapy dose or switching to other regimens. The Food and Drug administration (FDA) now takes into consideration patient-reported outcomes for approval of new therapeutic interventions [10], and recognition by the FDA has led to PROMs being more frequently utilized as a surrogate endpoint in clinical trials [11].

QoL can also be captured with objective measures such as evaluation of body composition and mobile-device controlled actigraphy monitoring. Furthermore, with the advent of smartphones and watches, researchers now also have the ability to track patient well-being and or toxicity throughout the trajectory of care. The ability to intervene in "real time," such as by integrating novel interventions like virtual mentoring coupled with virtual reality, may well drastically change how QoL metrics are defined and utilized during treatment. While the focus of the chapter is on QoL, it is important to note that other objective measures of the patient's status exist such as lab values (e.g., albumin, tumor biomarkers), imaging (e.g., sarcopenia, radiomics), vitals, and body mass index (BMI). A holistic approach to patient care with true integration of QoL metrics and the aforementioned objective measures will help better characterize the needs and burden of patients leading to improved overall care of the patient, and potentially translate into improved outcomes (Fig. 28.1).

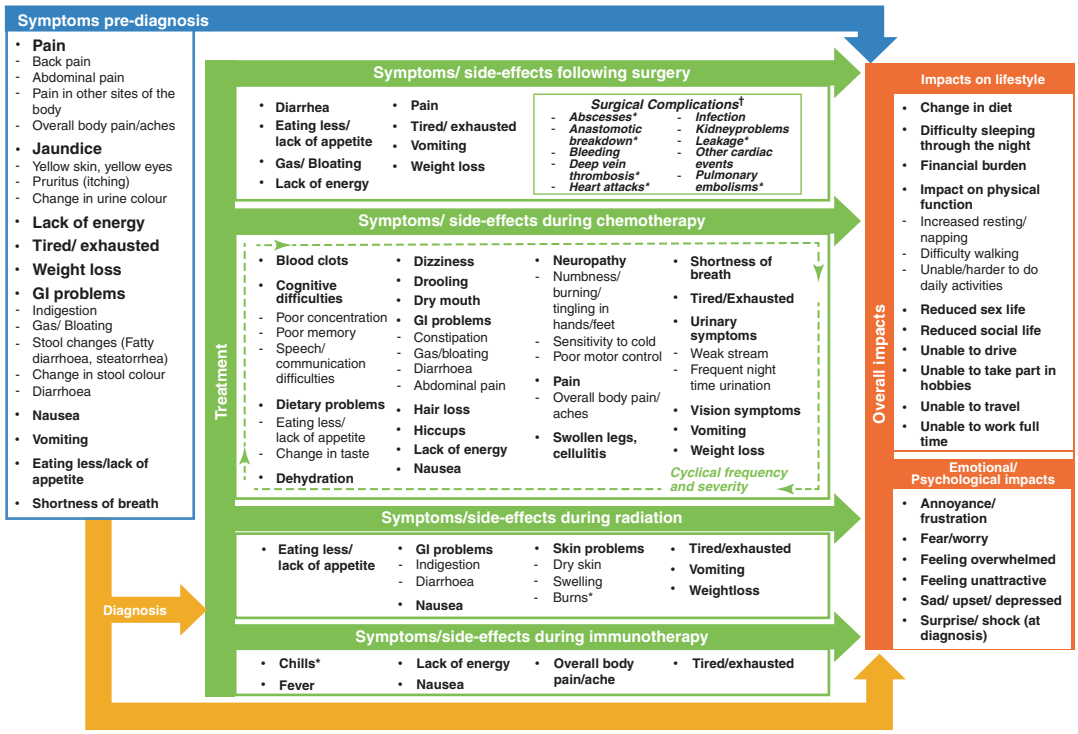


Fig. 28.1 Conceptual model of patient's experience of pancreatic cancer diagnosis and treatment [12]

Potential QoL Tools That Can Be Optimally Implemented for Patients with PDAC

The choice of which QoL tools or PROMs to administer in a study or utilize for patient care should be well thought out and with the patient at the center (Fig. 28.2). These measures should be used to assess the severity of patients' symptoms, monitor global QoL, and composite clinical benefit scores while managing patients' symptoms in real time. There are many factors that may influence the reliability of the information gathered through such assessments, including education and literacy level, preferred language of the patient, how it is administered (paper or online); and the environment in which it is administered (clinic or at home). Moreover, although there are many such tools, only a few have been externally validated. Although non-validated tools may be easier to administer and complete for patients, they should not be used as a primary endpoint in a trial as the significance of results acquired by non-validated tools remain unclear. The value to patients with non-validated tools has yet to be fully characterized.

An example of a HrQoL tool that has been commonly used for various diseases is the National Institute of Health's Patient-Reported Outcome Measurement Information System (PROMIS) tool [14]. Examples of common validated HrQOL tools specific to cancer include the European Organization for Research and Treatment Quality-of-Life Core Questionnaire (EORTC QLQ-C30) and its site-specific subset for the pancreas (PAN26), and the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General (FACIT-TS-G) [15–17]. These tools have also been validated in various settings for PDAC. For example, PROMIS and the EORTC QLQ-C30 have been previously validated in patients with metastatic PDAC [18, 19]. FACIT-TS-G scores have also been used as endpoints in trials for metastatic PDAC [20]. The QLQ-C30 (global) and QLQ-PAN26 (site specific) have been used in the unresectable setting in a multicenter stereotactic body radiation therapy (SBRT) study [7, 21]. In early stage PDAC treated with adjuvant or neoadjuvant chemotherapy, the most common tools utilized were the EORTC QLQ-C30 and PAN26 [22].

It can be challenging to know which QoL tool is ideal for a specific need, and which PROM selection for study design will be ideal in its ability to capture the intended changes in the specific patient population. For example, Herman et al. used both generic and PDAC-specific HrQoL tools (i.e., EORTC-QLQ-C30 and PAN26) to demonstrate that the addition of stereotactic body radiation therapy (SBRT) to pancreatic cancer did not change patients' global QoL while also improving their pain [21]. We therefore reviewed the most commonly utilized QoL tools and PROMs in PDAC and provide an overview of the ones felt to provide the most clinical utility for PDAC patients as summarized in Table 28.1. For research protocols, we recommend that investigators consider using these QoL tools in Table 28.1 for patient and caregiver evaluation at baseline, at specified time points during treatment, and at each follow-up. Ideally, the FH&RF questionnaire could be given at baseline and the FACIT-TS-G can be given at 4 and 12 months. Of note, caregiver reports should be tracked and deemed acceptable as an alternative for PROMs if the patient cannot self-complete the surveys. Additionally, a comprehensive family history questionnaire and Daily Status Log are other PROMs that can be used to further characterize the patient experience.

These tools should be used by investigators to better capture the patient perspective in characterizing the safety and effectiveness of various treatment regimens for PDAC, and to use as a guide for consideration of what modifications may be needed in the future. In addition, utilization of these tools in the clinic should improve symptom management and lessen any stresses and anxieties that pancreatic cancer patients experience as a result of illness and treatment. Consideration should be given to capturing responses on mobile devices or computers so that the responses are available in real time for pro-

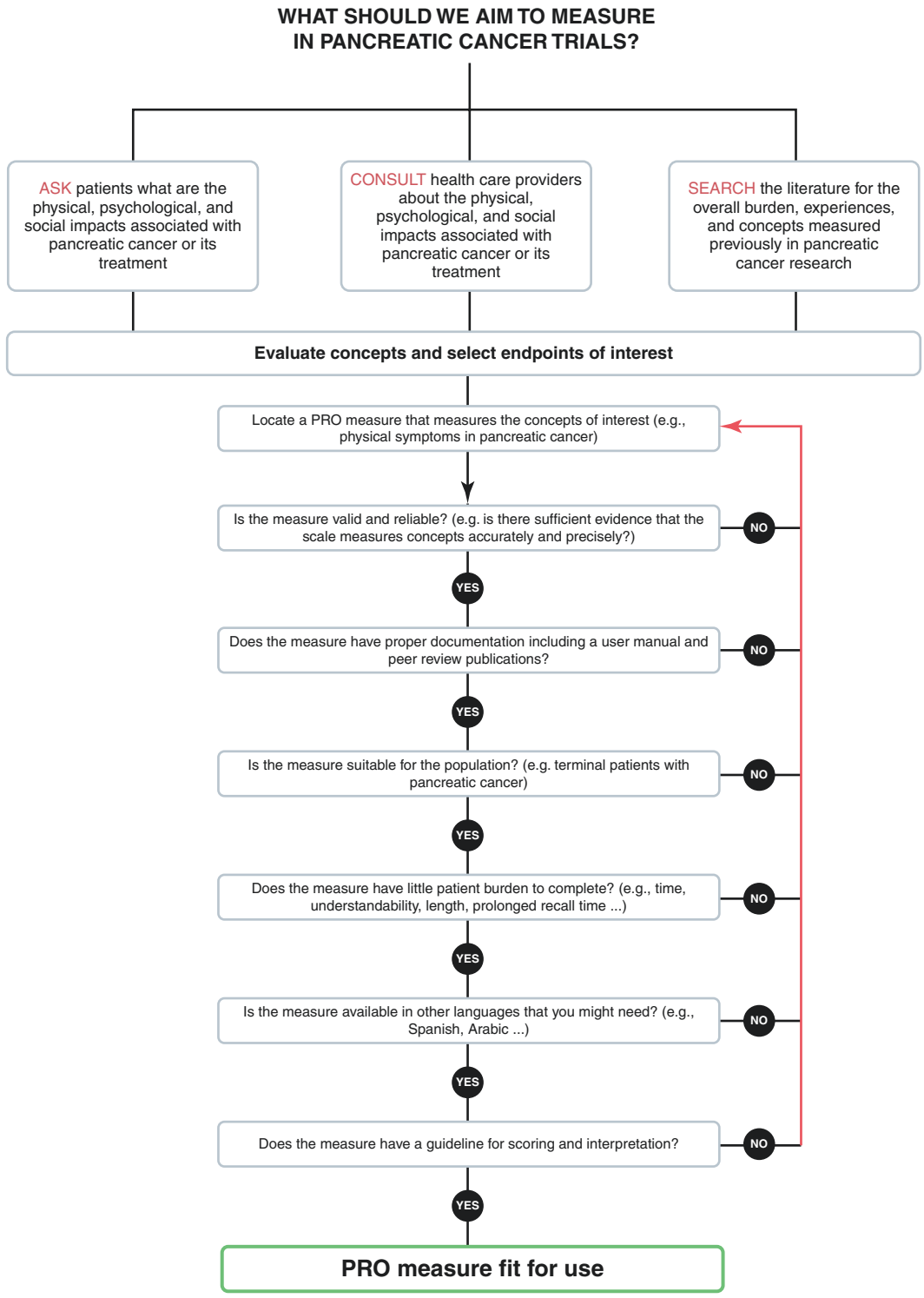


Fig. 28.2 Patient-reported outcome (PRO) measure selection [13]

Table 28.1 Description of potential PRO questionnaires for PDAC

PRO questionnaire	Description	Measure	Why chosen, significance
European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 [15]	30-item rating scale including nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale	Patient QOL, toxicity, symptom distress	• Very meaningful to our PRPs • Previous collaborative experience using these at JHU, Stanford, and MSKCC • Widely used to evaluate QOL in cancers and well-liked • Used in previous SBRT and FOLFIRINOX studies [16–18]
European Organization of Research and Treatment of Cancer (EORTC) QLQ-PAN26 [17]	26-item rating scale related to disease symptoms, treatment side effects, and emotional issues specific to PDAC	Patient QOL, toxicity, symptom distress	• Very meaningful to our PRPs • Individual questions can be used to determine stage and outcomes • Previous collaborative experience using these at JHU, Stanford, and MSKCC • Used in previous SBRT and FOLFIRINOX studies [16–18]
Patient-reported outcomes measurement information system (PROMIS) 29 [16]	29-item rating scale of 7 core domains (physical function, anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, pain interference) as well as one 11-point rating scale for pain intensity	Patient QOL, toxicity, symptom distress	• Key factors to optimizing care per our PRPs (pain, anxiety, depression especially) • Widely used in other PCORI and oncology studies, external validation
Brief assessment scale for caregivers (BASC) of the medically ill [23]	14-item rating scale measuring burden and QOL, plus 8-item subscale measuring negative personal impact	Caregiver QOL, symptom distress	• Very important to and selected by our team of PRPs • Limited data on this topic for PDAC
Functional assessment of chronic illness therapy-treatment satisfaction—general (FACIT-TS-G) [24]	8-item rating scale measuring overall evaluation of current treatment and patient experience	Treatment satisfaction	• Important given poor PS and short life expectancy • Contributes to improving patient-centered care • Can be used to make modifications to future regimens
Family history and risk factors (FH&RF) questionnaire	9-item questionnaire designed to evaluate family history and predisposing risk factors	Family history, risk factors	• Insightful into future methods to detect PDAC earlier • Can combine these measures with biomarker profile to predict outcome • Can relieve stress of patient and family members
Daily status log	Personalized tool designed to monitor daily status and progress (i.e., weight, troubling symptoms, energy level, physical activity level, and comments)	Patient QOL, symptom distress	• Designed by our team of PRPs • Personalized to patient-specific needs • Can help patient, caregiver, and clinical team

viders to review. This can lead to improved patient-physician communication and providers can address any concerns and manage symptoms more efficiently and effectively.

Associated Tools to Collect Patient Reported Outcomes

Actigraphy (wearables) has become a promising method for obtaining and measuring patient-reported outcomes in clinical cancer research. Many clinical trials have utilized wearable activity trackers to collect data in real time and assess a patient's quality of life throughout their course of treatment. Data obtained from wearable devices can be used to predict clinical outcomes by monitoring different activity patterns simultaneously, including sleep parameters [25, 26], heart rate [27], and steps per day [27–29]. These devices provide patients an avenue to track their own health and can encourage them to engage in physical activity through regular prompts and feedback [29, 30]. Although wearable activity devices present a greater upfront and long-term cost than other quality of life measures, such as patient reported outcome questionnaires and surveys, these devices provide a method for objective data collection that is not influenced by a patient's expectations, recall bias or memory impairments.

The use of wearable devices, such as the physical activity monitors made by Fitbit, have been correlated with improvements in quality-of-life measures for cancer patients [29, 30]. In addition to improving objective data collection, wearable devices have helped reduce health care costs by reducing odds for adverse events and hospitalizations in advanced cancer patients [28]. While there are no currently published actigraphy studies for pancreatic cancer patients in particular, the efficacy of wearable devices in other cancer trials suggest similar benefits may be seen in the pancreatic cancer patient population [31]. Difficulty getting patients to consistently wear activity trackers and tracker accuracy are other areas of concern, although device accuracy has been steadily improving over time [32, 33]. Ultimately, wearable activity trackers may be most useful as a supplement to other quality of life measurement tools, rather than a standalone method of data collection for cancer patients.

Challenges in Implementing QoL Measures Into Clinical Trials

There are several challenges that researchers face in implementing an effective QoL element in their research or clinical trial. In a systematic review of available PRO studies (not specific to cancer), challenges included the fact that (1) PRO-specific guidance is difficult to access in real time, (2) QoL measures lack consistency and are often unwieldy, (3) results and interpretations are not standardized, and (4) statistical interpretations are varied and missing data is common [34]. Like other endpoints such as survival, we recommend that the methodology of analyzing data with PRO should be determined a priori and included in the protocol and manuscript. The methodology should include how missing data will be handled, which is a common phenomenon in PDAC given the risk of early patient progression. The lack of standardization with PROM with variations in scale, measurement, and interpretation can make it difficult to reach conclusions when results from clinical trials are evaluated. For example, some metrics can indicate favorable results with higher values whereas others may indicate favorable results with lower values. The determination of appropriate time points to assess clinically meaningful changes with QoL tools can be difficult. Furthermore, for pancreatic cancer, it is therefore extremely challenging to implement PROs into daily practice because studies are often small and not powered to demonstrate statistically meaningful differences.

Both the European Medicines Agency (EMA) and the FDA have attempted to address these issues in guidance provided to researchers [31, 35]. The focus of this guidance is primarily on the registration process of new drugs and pharmaceuticals. The 2005 EMA paper recommends that clinical trials have dual HrQoL evaluation and efficacy endpoints. The FDA guidance also highlights the importance of incorporating PRO measures into trials to help improve the validity and relevance of the results to the patients enrolled in the study. In the last 20 years, QoL research has progressed significantly since the EMA and FDA papers (2005 and 2009, respectively). However, the core criticisms indicated above remain largely unaddressed.

Statistical Challenges and Opportunities Related to QoL Analyses

Longitudinal and Cross-Sectional Studies

When reviewing clinical reports, it is important to recognize if the QoL tool was administered at one cross-sectional time point or over multiple longitudinal time points. If longitudinal, a generalized estimating equation (GEE) or random effects model should be used for the analysis.

Using QoL Studies to Compare Arms

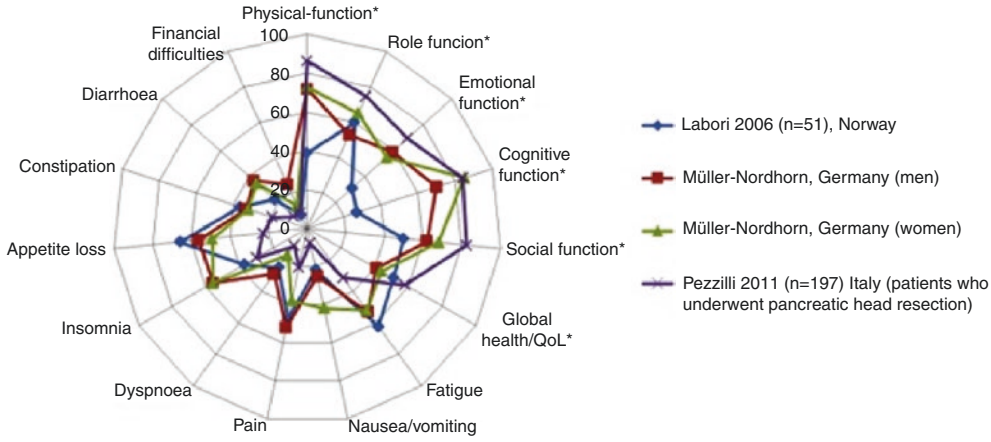
Finding a statistically significant difference using QoL tools can be difficult given smaller sample sizes common in PDAC studies. That is why a "clinical significance" cut-off is often defined prior to the study to identify an "important" clinical/meaningful difference (positive or negative) of an intervention or comparison of interventions. Another approach used by Anota et al. was the HrQoL deterioration-free survival (QFS), defined as the time from randomization to a first significant deterioration as compared to baseline score with no further significant improvement or death [36]. To help balance groups, propensity scores can be used, and multivariate cox regression analyses can identify independent factors influencing QFS [36].

Statistical Presentation

In addition to standard tables outlining QoL and PRO responses, spider plots can be very helpful in understanding how a specific treatment (before, during, and after) influences QoL as well as comparing QoL between treatment arms. For example, Carrato et al. [5] summarized five studies using a spider plot based on reported HrQoL data as demonstrated in Fig. 28.3 [37–41].

Options to Address Missing Data

Unfortunately, missing data is common in pancreatic cancer studies because a large proportion



Note: In the first 6 function scales a high score = better level of functioning, whereas a high score on symptom scale/single item = worse symptoms

Fig. 28.3 Example of spider plot of QoL symptoms [5]

of patients become ill or die earlier than anticipated thus preventing them from completing the forms longitudinally [42]. Researchers should partner with statisticians to incorporate validated methods to account for missing data that can result in statistical uncertainty. One approach is to use multiple imputation as described in Rubin or a rank-based approach [43]. A sensitivity analysis can also be helpful when there is missing data [44]. This is where different missing data imputation techniques can be employed and the results of each can be qualitatively compared. If results differ significantly based on the type of missing data, imputation techniques are used, and additional analyses or comparisons may be needed to explain the cause(s).

The use of the propensity score in conjunction with the time until definitive deterioration (TUDD) method can reduce the bias due to the occurrence of missing data depending on patients' characteristics during follow-up [45]. Multiple imputations on the HrQoL scores could also be performed but this method requires a larger sample and can only include one or two factors associated with missing data [38], but more variables can be retained in the propensity score. This approach could be considered for use in trials with limited sample sizes. Contrary to the pattern mixture models, the inverse probability of treatment weighting (IPTW) method in conjunction with the TUDD approach is optimal for oncology clinical trials, for which a lot of HrQoL measures are done. In fact, the number of possible patterns increases with the number of HrQoL measures. Austin et al. recommended use of IPTW for time to event data [46]. Finally, the IPTW method is easy to understand (weighting observations according to the presence or absence of missing data) [46].

QoL Clinical Studies

In patients with PDAC, QoL, PS, and pain should be assessed at baseline to better understand whether any intervention provides benefit or harm. Subsequent clinical visits should document whether these measures changed over time, ideally in a structured way. In a clinical trial this is often done as part of the study and at specific intervals centered around re-staging. Outside of a clinical trial quality of life is often less structured and more challenging to ascertain a change from baseline. Using structured notes in an EMR can help remind healthcare teams to reassess performance status, pain, and quality of life but missing data are still common. Using apps and/or questionnaires that can be administered electronically can minimize missing data and lead to more complete and often accurate information. However, electronic forms can sometimes be more challenging for elderly patients or those who are less educated.

A comprehensive systematic review of QoL in adults with PDAC and their caregivers was recently conducted and, again, showed significantly poorer HrQoL scores for PDAC patients compared to population norms and a loss of 610,000–915,000 QALY annually with PDAC [5]. This was confirmed in another systematic review of the literature where PDAC patients were also compared with healthy adults or population norms: adults with pancreatic cancer had worse QoL across most domains [47]. In addition, compared with other cancer types, patients with PDAC also reported worse psychological symptoms [47]. This is likely due to the poor prognosis of PDAC and its known association with depression. Physical and social QoL symptoms are either similar or even more compromised than in patients with other cancers. QoL studies related to sexual, spiritual, and caregiver QoL are limited and desperately needed. In fact, depression and anxiety are common in patients with advanced PDAC [37–39]. In a Norwegian population, 42% of patients had moderate or severe anxiety and depression [40]. In a German study, the number of patients experiencing anxiety/depression was approximately tenfold higher than the normal population [38]. Moningi et al. looked at how clinical factors correlated with quality of life (QoL) questionnaires administered to patients presenting to the Johns Hopkins Pancreas Multidisciplinary Clinic (PMDC) with various stages of disease [7]. The study examined associations between disease status, PFS, and QoL responses in order to identify patient subgroups

that were most at risk for reduced QoL using the QLQ-PAN26 questionnaire [7]. They found that patients with a worse performance status, defined as ECOG > 1, were significantly more likely to report symptomatic pancreatic pain ($P > 0.001$), digestive symptoms ($P > 0.017$), cachexia ($P > 0.004$), and ascites ($P > 0.001$) compared with patients with a performance status of 0 [7]. The majority (92%) of patients reported a significant fear of future health problems, regardless of disease status or performance status [7]. A summary of the key randomized trials in PDAC that incorporate PRO as an endpoint is presented in Table 28.2.

Table 28.2 Key randomized studies that incorporate QoL as an outcome in pancreatic adenocarcinoma

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Polistina, 2010, Ann Surg Oncol [48]	23 patients with LAPC undergoing SBRT, assessing treatment response, local control, pain, and QoL	SF-36	No QoL differences between pretreatment, 3-month, or 6-month follow-ups	
Quan, 2018, Pract Radiat Oncol [49]	Phase 2 clinical trial with 35 patients with either BRPC or LAPC assessing induction chemo followed by SABR	FACT-G	No QoL differences between pretreatment, post-chemo, SABR, or surgery	
Krempien, 2005, BMC Cancer [50]	Phase 2 clinical trial with 66 patients LAPC evaluating Cetuximab and IMRT	QLQ-C30, QLQ-PAN26	N/A	
Morak, 2010, Cancer [51]	Prospective study comparing QoL between 120 patients with or without adjuvant CRT	QLQ-C30	Better QoL scores for patients with neoadjuvant CRT versus control	
Knaebel, 2005, BMC Cancer [52]	Phase 3 clinical trial with 110 patients comparing adjuvant 5-fluorouracil, cisplatin, interferon alpha and radiation versus folinic acid and 5-fluorouracil	QLQ-C30, QLQ-PAN26, CES-D	N/A	
Herman, 2015, Cancer [21]	Phase 2 clinical trial with 49 patients with LAPC evaluating Gemcitabine and SBRT	QLQ-C30, QLQ-PAN26	Stable QoL scores from baseline to post-SBRT, improvement in pain scores post-SBRT	
Serrano, 2014, Int J Radiat Oncol Biol Phys [53]	Phase 2 clinical trial with 55 patients with PDAC evaluating QoL during and after neoadjuvant CRT and surgery	QLQ-C30, QLQ-PAN26, FACT-Hep	Temporary increase in GI symptoms and decrease in physical functioning after neoadjuvant CRT. QoL returned to baseline after surgery	
Short, 2013, Int J Radiat Oncol Biol Phys [54]	Phase 2 clinical trial with 63 patients with PDAC evaluating QoL using 3D conformal CRT sandwich technique	QLQ-C30, QLQ-PAN26	Stable QoL, improvement in local symptoms for CRT	
Katz, 2017, BMC Cancer [55]	Phase 2 clinical trial with 134 patients with PDAC comparing mFOLFIRINOX versus mFOLFIRINOX with SBRT	PRO-CTCAE	N/A	
Haddock, 2007, J Clin Oncol [56]	Phase 2 clinical trial evaluated QoL differences for 48 patients with LAPC who received Gem-CRT or Gemcitabine alone	SDS LASA	No QoL difference between baseline and final measurement, however certain measures improved (outlook, insomnia, pain)	

Table 28.2 (continued)

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Heras, 2009, Am J Ther [57]	Prospective study comparing QoL differences for 30 patients with unresectable PDAC who received RT with 5-FU or RT with gemcitabine	QLQ-C30	Overall QoL improved for both groups with RT	
Hurt, 2015, Int J Radiat Oncol Biol Phys [58]	Phase 2 clinical trial evaluated QoL differences for 114 patients with LAPC who received gemcitabine plus capecitabine and either Gem-CRT or Cap-CRT	QLQ-C30, QLQ-PAN26	Initial QoL improvement at start of CRT, decline during CRT, and return to baseline post-CRT	
Loehrer, 2011, J Clin Oncol [59]	ECOG clinical trial with 74 patients with unresectable PDAC evaluating QoL differences between Gem-CRT versus Gemcitabine alone	FACT-Hep	No QoL difference between groups, both groups showed decline in QoL over treatment period	
Moore, 2007, J Clin Oncol Off J Am Soc Clin Oncol [60]	Phase 3 clinical trial comparing 569 PDAC patients with either erlotinib plus gemcitabine or gemcitabine alone	QLQ-C30	No QoL difference between groups (except worse diarrhea in Gem+Erlotinib group)	
Neoptolemos, 2001, Lancet [61]	Randomized control trial with 541 patients with resectable PDAC evaluating adjuvant CRT and chemotherapy	ESPAC-1 QoL	Improved QoL for adjuvant CRT and Chemo versus control	
Neoptolemos, 2017, Lancet [62]	Phase 3 clinical trial comparing 732 patients with resected pancreatic cancer who received either gemcitabine plus capecitabine or gemcitabine alone	QLQ-C30	No effect on QoL by treatment group	
Oettle, JAMA, 2007 [63]	Randomized control trial evaluating role of adjuvant gemcitabine for 368 patients with resected pancreatic cancer	Spitzer QL-Index	QoL improvement for both groups, no difference between groups	
Conroy, NEJM, 2018 [64]	Phase 2 and Phase 3 clinical trial comparing 493 patients with resected pancreatic cancer who received FOLFIRINOX and gemcitabine	QLQ-C30	No QoL differences between 5-FU and gemcitabine groups	
Deng, 2018, Euro J Cancer [65]	Hospital-based cohort of racially/ethnically diverse patients with PDAC	Short-form 12, including PCS and MCS	Hispanics at significantly higher risk of lower PCS and MCS compared to non-Hispanic whites; stage III and IV patients with lower PCS than stage I patients	
Crippa, 2008, J Gastrointest Surg [66]	92 patients with different stages of PDAC who underwent surgical and/or medical intervention	Functional assessment of cancer therapy questionnaire	Surgery favorably impacts quality of life (patients who underwent surgical resection had improved QOL), whereas chemotherapy/chemoradiation did not significantly modify QOL	

(continued)

Table 28.2 (continued)

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Al-Batran, 2021, Int J Cancer [67]	601 patients treated with Nab-paclitaxel/gemcitabine	QoL/global health score	Patients improved or maintained QoL after 3 and 6 months, and QoL is predictor of outcome	
Mackay, 2020, JNCCN [68]	100 patients with newly diagnosed pancreatic or periampullary cancer	IN-PATSAT32 and QLQ-C30	Satisfaction with care, but not QoL, decreases after treatment. QoL factors not independently associated with patient satisfaction	
Gourgou, 2012, J Clinical Oncology [19]	342 patients assigned to take FOLFIRINOX or gemcitabine	QLQ-C30	FOLFIRINOX significantly reduces QoL impairment compared to gemcitabine for metastatic pancreatic cancer patients	
Troger, 2014, Deutsches Arzteblatt International [69]	220 patients with locally advanced or metastatic pancreatic cancer who were only receiving supportive care, divided into groups that received mistletoe extract or not	QLO-C30	Mistletoe extract significantly improved QoL compared to supportive care alone	
Bernhard, 2009, J Clinical Oncology [70]	Patients assigned to receive GemCap or Gem	CBR criteria and Karnofsky performance status	No difference in CBR or QoL between GemCap and Gem	
Wong, 2004, JAMA [71]	100 patients with unresectable pancreatic cancer with pain assigned to neurolytic celiac plexus block vs. opioids alone	Pain intensity (0–10), QoL scores	NCPB improves pain relief but does not affect QoL	

QoL Studies in Resectable Disease and Prior to Surgery

Surgery studies incorporating QoL in general tend to be cross sectional instead of longitudinal which is a significant limitation [72, 73] because it does not allow us to gather sufficient information about the temporality of the observed phenomena. This precludes us from proposing causal pathways between psychological predictors of QoL and psychological distress. Future research should use a longitudinal design to (1) identify other important psycho-logical predictors of preoperative and postoperative psychological distress and QoL and (2) distinguish the proper effect of surgery from the psychobiological effect of pancreatic cancer on depression.

In a review of nine studies with QOL and other psychological factors post-pancreatectomy, the authors showed that although quality of life initially declined postoperatively, it significantly improved 3–6 months after surgery [74]. Regarding the postoperative experience, one study reported that there was a high fear of cancer recurrence [74]. One study explained how the ability to adapt to the diagnosis of PDAC was mainly influenced by the age and the subjective experience of the patients [74]. Interestingly, depression did not appear to affect survival rate after surgery [74]. Only a few studies have characterized the psychological experience of patients as it relates to surgery and there remains a need for more studies to describe and characterize the patients' psychological characteristics in this setting.

In patients with resectable pancreatic cancer, QoL studies can help in determining if patients are good surgical candidates and/or identify areas that may need attention perioperatively. Ngo-Huang et al. at MD Anderson Cancer Center investigated relationships among physical activity, physical function, and QoL among patients with patients with resectable PDAC enrolled in a home-based exercise rehabilitation program [75]. Patients with resectable PDAC receiving preoperative chemotherapy and/or chemoradiation were advised to perform ≥60 min each of moderate-intensity aerobic exercise and strengthening exercise weekly. Increased weekly light physical activity was associated with increased HrQoL [75]. Patients with potentially resectable pancreatic cancer exhibited meaningful improvement in physical function with rehabilitation, and, in turn, physical activity was associated with improved physical function and HrQoL [75]. This data highlights the importance of physical activity during treatment for pancreatic cancer and its potential benefit in improving QoL.

QoL in Adjuvant Therapy Studies

Results from one of the seminal trials in the adjuvant setting, the European Study Group for Pancreatic Cancer-1 Trial (ESPAC-1), which compared adjuvant chemotherapy to chemoradiation (CRT), demonstrated that the potentially negative effects on QoL with therapy should be considered in addition to any improvement in survival to get a more comprehensive picture of the efficacy of the intervention [62, 76]. Interestingly, in the subset of patients (n = 316) who were followed longitudinally for QoL outcomes with the EORTC-QLQ-C30, when survival was integrated with QoL the Quality Adjusted Life Months at 2 years (QALM-24) post-surgical resection was lower for both chemotherapy (17.3 vs. 9.6 months) and CRT (15.5 vs. 7.1 months) compared to 2-year survival without integration of QoL [62, 76]. Ultimately, however, the difference in QoL outcomes between the chemotherapy and CRT arms were not significant. It should be noted that this trial used inferior chemotherapy regimens (i.e., single agent 5-Fluorouracil), and antiquated radiation techniques with a split course regimen and prescribed doses that are now known to be inadequate for disease control.

In addition, QoL measures have been used to assess the therapeutic benefit and safety of chemotherapy in the adjuvant setting. One example is a phase 2 prospective study evaluating the addition of erlotinib in combination with adjuvant chemoradiation and chemotherapy for resected PDAC [77]. In this study 48 patients received adjuvant erlotinib and capecitabine twice daily concurrently with intensity modulated radiation therapy (IMRT) to 50.4 Gy in 28 fractions followed by four cycles of gemcitabine and erlotinib. QoL was assessed with the EORTC QLQ-C30 and the QLQ-PAN26 just before CRT initiation or during the first week of its administration, between completion of CRT and starting maintenance chemotherapy, and within 3 months after completion of maintenance chemotherapy [77]. The mean global QoL scores remained stable throughout both phases of treatment, and there were no significant changes in 4 of the 5 functional QoL scales (role, cognition, emotional, and social), although physical function score declined slightly (by 6.2 points) during CRT. Symptoms of pain, fatigue, nausea/vomiting, dyspnea, insomnia, and constipation did not change significantly from baseline [77]

Neoadjuvant and Definitive Therapy: Resectable, Borderline Resectable, and Locally Advanced Pancreatic Cancer

Most reports describing the tolerability of radiation in pancreas cancer are derived from physician-assessed toxicities using RT techniques that are either outdated or expose greater volumes of normal tissue to radiation with limited supportive care. These older studies often combine RT with more aggressive chemothera-

pies including bolus 5-FU or higher doses of concurrent gemcitabine, thus increasing treatment related toxicities (often GI) and decreasing quality of life. For example, in ECOG 4201, patients with LAPC were randomized to full dose gemcitabine (1000 mg/m^2) alone or chemoradiation with a lower dose of gemcitabine (600 mg/m^2) combined with standard fractionated radiation (50.4 Gy over 5.5 weeks) [59]. Although the study was closed prior to reaching its planned accrual, there was a significant improvement in survival in patients receiving combined gemcitabine and radiation [59]. Although there was an improvement in survival with CRT, patients who received combined chemoradiation had substantially more grade 4 toxicity (41.2 vs. 5.7%; $p < 0.000$) compared to those who were treated with gemcitabine alone [59].

Since the ECOG 4201 study, reported rates of RT associated grade 3–4 toxicity have declined in part due to improvements in RT planning (IMRT), decrease in target volumes, avoidance of organs at risk (OAR) using a planning OAR volume (PRV), image guidance (CT on rails, MRI), advancements in nutrition (enzymes), and proactive supportive care. A more recent trial in the LAPC setting, the LAP07 trial (gemcitabine and CRT vs. gemcitabine alone), used 3D-CRT (tumor plus a margin but no elective nodal coverage) with concurrent capecitabine, grade 3+ toxicity was similar to the group that received chemotherapy alone (20%) [78]. Recent trials in the resectable and borderline resectable pancreatic cancer (BRPC) setting, such as the PREOPANC-1 trial which compared upfront surgery vs. neoadjuvant CRT, showed improved survival outcomes in the CRT arm without any significant increase in grade 3+ toxicity [55]. The Alliance trial A021101 prospectively treated BRPC patients with CRT (tumor plus margin, not covering ENI) but with more aggressive systemic therapy with FOLFIRINOX (FFX) at several high-volume centers [79]. Although grade 3+ toxicity was 43%, most toxicity was thought to be attributed to FFX chemotherapy as opposed to the radiation [79]

However, to date, most trials have not consistently reported on QoL metrics in the neoadjuvant or definitive settings. Breen et al. reported on a multi-center prospective registry evaluating the effect of CRT on patient-reported QoL for patients with intact and localized PDAC [80]. QoL was assessed pre-CRT (immediately before CRT and after neoadjuvant chemotherapy) as well as at the completion of CRT with FACT-Hep and its component parts: FACT-General (FACT-G) and hepatobiliary cancer subscore (HCS) [80]. A minimally important difference from pre-CRT was defined as $\geq$ 6, 5, and 8 points for FACT-G, HCS, and FACT-Hep, respectively [80]. Approximately 40% of patients had BRPC whereas 57% had LAPC [80]. FFX (75%) or gemcitabine and nab-paclitaxel (GnP, 42%) were given for a median of six cycles (range, 0–42) before CRT [80]. Radiation therapy techniques included 3-dimensional conformal (22%), intensity modulated photon (55%), and intensity modulated proton (23%) radiation therapy to a median dose of 50 Gy (range, 36–62.5) [80]. Concurrent chemotherapy was most commonly capecitabine (82%) [80]. Sixty-three patients (63%) had surgery after CRT [80]. The mean decline in FACT-G, HCS subscale, and FACT-Hep from pre- to post-CRT was 3.5 (standard deviation [SD], 13.7), 1.7 (SD 7.8), and 5.2 (SD 19.4), respectively [80]. Each of these changes were statistically significant, but did not meet the minimally important difference threshold [80]. Pancreatic head tumor location was associated with decline in FACT-Hep on MVA [80]. Nausea was the toxicity with the greatest increase from pre- to post-CRT by both physician-assessment and patient-reported QoL [80]. Interestingly, type of radiation modality did not significantly alter the QoL changes, but the numbers were small [80].

One of the concerns of long course CRT is that patients are not receiving full dose systemic therapy and therefore may be at an increased risk of metastatic spread. A prospective, phase 2 multi-institutional trial evaluated a regimen using full dose chemotherapy (gemcitabine and oxaliplatin) with a more focused and lower dose RT

(tumor plus a 1–1.5 cm margin, 30 Gy in 15 fractions) given concurrently with the first cycle of chemotherapy in patients with mostly resectable and BRPC [81]. Patients completed the EORTC-QLQ C30, EORTC-PAN 26, and FACT-Hep at baseline, after two cycles of neoadjuvant therapy, after surgery, at 6 months from initiation of therapy, and at 6-month intervals for 2 years [81]. A change >10% in mean score compared to baseline was considered a minimal clinically important difference [81]. The EORTC-QLQ C30 global QoL did not significantly decline after neoadjuvant CRT with full dose chemotherapy, whereas the Functional Assessment of Cancer Therapy global health measure showed a statistically, but not clinically significant decline (−8, P = 0.02) [81]. This was in parallel with deterioration in physical functioning (−14.1, P = 0.001), increase in diarrhea (+16.7, P = 0.044), and an improvement in pancreatic pain (−13, P = 0.01) as per EORTC-PAN 26 [81]. Because of poor patient compliance in the nonsurgical group (no longer followed after progression), long-term analysis was performed only on surgically resected participants (n = 36) [81]. The authors found that the first 2 months of systemic therapy was completed without a clinically significant QoL deterioration [81]. A transient increase in gastrointestinal symptoms and a decrease in physical functioning were seen after neoadjuvant chemoradiation [81]. In those patients who underwent surgical resection, most domains returned back to baseline levels by 6 months [81]. The study also highlighted the challenge of missing data in these studies, especially when patients progress and come off study. Using smaller volumes with modern technology that limits the dose of RT to the bowel complemented by more aggressive management of symptoms can improve QoL while receiving aggressive multimodality treatment. There also appears to be a good correlation with GI toxicity and a decline in QoL with both the EORTC and FACT questionnaires.

Other approaches are also currently being investigated for the potential to improve QoL such as (1) decreasing the size of the radiation treatment volume by using motion management (breath-hold, tracking), (2) increasing visualization (MRI/fiducials), (3) decreasing the number of fractions a patient receives (1–5 vs. 25–30). More sophisticated radiation techniques have the potential to improve QoL metrics as well. Bittner et al. found that IMRT was associated with lower rates of grade 3+ acute nausea ± vomiting, diarrhea, and late GI AEs [82]. This suggests that limiting dose to bowel correlates with less toxicity and improved QoL. Jethwa et al. reported on their initial experience with intensity modulated proton therapy (IMPT) for intact pancreas cancer [83]. Although a small study (N = 13), patients completed the FACT-Hep questionnaire prior to CRT and at the end of CRT. The FACT-Hep score dropped by a median of −7.5 (P = 0.18) [83]. The FACT-Gen dropped by a mean difference of −6.3 (P = 0.09). The authors concluded that there were low rates of acute GI AEs and no significant change of PROs from baseline suggesting further exploration of IMPT in localized PDAC [83].

SBRT is another technological advancement in radiation technique that has significantly decreased acute side effects when compared to CRT. SBRT is given over 1–5 treatments, covers smaller volumes (typically gross tumor volume plus 3–5 mm margin) and is typically delivered without concurrent chemotherapy. Koong et al. was the first investigator to evaluate single-fraction SBRT in the treatment of LAPC [84]. A single dose of 25 Gy effectively palliated symptoms with nearly 100% local progression-free survival (LPFS) at 1 year [84]. While acute GI toxicity was acceptable, late GI toxicity was high (~40%) [85]. To improve patient OS while limiting toxicity Herman et al. conducted a multicenter phase II study to test the safety and efficacy of adding fractionated SBRT (6.6 Gy × 5) to full-dose gemcitabine (SBRT given after 1–3 doses) in patients with LAPC [21]. This prospective study enrolled 49 LAPC patients with KPS >70 and a median age of 67.9 years [21]. One- and two-year OS was 61% and 18%, respectively, while mOS was 13.9 mos [21]. Four patients

(8.2%) with LAPC underwent margin- and node-negative resections following gemcitabine (GEM) +SBRT [21]. Rates of acute and late grade ≥2 gastritis, enteritis, or ulcer toxicities were 2% and 11%, respectively [21]. Acute toxicity included: grade 2 anorexia (37%), fatigue (28%), nausea (22%), abdominal pain (19%), weight loss (9%), diarrhea (3%); grade 3 nausea (9%); and grade 4 nausea (6%) [21]. Late grade ≥3 GI toxicity appeared to have improved at 9% with fractionated SBRT compared to historical outcomes [21]. Mean QoL score 4 weeks post-SBRT was similar to baseline ($p = 0.38$) [21]. In fact, at 6 months there was a trend towards improved QoL ($p = 0.07$) [21]. Overall, fractionated SBRT coupled with GEM achieved high rates of LPFS and tumor response. Minimal grade ≥3 acute and late toxicity was observed. It was determined that a combination of SBRT with more aggressive chemotherapy may further improve outcomes.

This led to a prospective non-randomized controlled phase II trial that investigated whether fractionated SBRT could be safely and effectively delivered in the setting of aggressive multi-agent chemotherapy (MA-CTX) [86]. This enrolled 48 patients between 2012 and 2015. The median follow-up after SBRT was 60 months among three patients still alive. Patients received MA-CTX with modified FOLFIRINOX (mFFX) or GnP followed by four fractions of SBRT (median 33 Gy). The primary outcome was the rate of late grade ≥2 gastrointestinal toxicity attributable to SBRT. Only one patient (2%) had late ≥ grade 2 gastrointestinal toxicity attributable to SBRT [86]. Neoadjuvant CTX duration was ≥4 months in 24 patients and 28 patients received mFFX [86]. Of 44 LAPC patients, 17 (39%) were surgically explored, and 12 (75%) achieved a margin-negative resection [86]. For all patients, the median overall survival (OS) was 21.6 months from diagnosis and 14.6 mo. from SBRT [86]. The 1- and 2-year OS from SBRT was 58% and 28%, respectively [86]. The study also evaluated the impact of fractionated stereotactic body radiation therapy (SBRT) on patient-reported quality of life (QoL) and physician-reported toxicity in patients with recurrent or locally advanced pancreatic cancer (PDAC) was prospectively evaluated. 42 PDAC patients had patient-and physician-reported outcomes prior to SBRT and 4–6 weeks post-SBRT [86]. Outcomes were consistently evaluated among both groups—performance status, fatigue, pain, anorexia, nausea, vomiting, constipation, and diarrhea. Patient-reported QoL metrics were assessed using a 4-point Likert scale on the EORTC QLQ-C30 and QLQ-PAN26, while physician-reported toxicities were graded using the NCI CTCAE version 4.0. Comparisons between those with paired patient-and physician-reported outcomes collected prior to and 4–6 weeks after SBRT were made using the Wilcoxon signed-rank test. A total of 29 had both patient- and physician-reported outcomes collected prior to and 4–6 weeks after SBRT. There was no significant impairment of any of the 8 physician-reported toxicities, nor were significant changes observed in patient-reported overall health ($p = 0.66$) or QoL ($p = 0.18$) scores following SBRT [86]. Patients felt less worried about their future health (mean change [mΔ] = −0.45, $p = 0.02$), and an improvement in feeling less attractive as a result of disease and treatment reached borderline significance (mΔ = 0.31, $p = 0.09$) [86]. However, patients felt limited in planning activities in advance (mΔ = 0.45, $p = 0.02$) and were more constipated (mΔ = 0.38, $p = 0.01$) 4–6 weeks post-SBRT [86]. Although the numbers are small, patients with unresectable or locally recurrent PDAC do not appear to suffer any detriment of overall health or QoL after receiving a 5-day course of SBRT. Moreover, this regimen may lead to a more optimistic point of view on future health and/or level of physical attraction.

Metastatic Disease

Several reports describe that QoL, toxicity, and symptom control all play a significant role in the well-being of patients with PDAC. This is especially important in patients with metastatic disease where the likelihood of cure is lower, and patients and caregivers want to balance quality and quantity of life. In the RESPONSE trial, an

important secondary endpoint was a composite score of "clinical benefit" as defined by Burris et al. [6]. This was one of the first studies to obtain FDA approval for a drug based on a non-survival endpoint. The PRODIGE 4 study, which evaluated FOLFIRINOX versus gemcitabine in the first-line metastatic setting, showed that FOLFIRINOX improved OS and HRQOL, despite the having worse toxicity than gemcitabine [64]. There were two earlier interventional studies in other chemotherapy combinations in the second-line setting, however, either did not report HRQOL (CONKO-003) or found no significant change between treatment arms (PANCREOX) [63, 87].

Anota et al. reported on sequential FOLFIRI.3 plus gemcitabine compared to gemcitabine alone in the first line metastatic setting [36]. They used the EORTC QLQ-C30 at baseline and every two months until end of study or death. The authors used the deterioration-free survival (QFS) propensity score analyses to balance arms, and MVA to look at other factors that may influence QFS. Specifically, the study used the IPTW propensity scoring method which is preferred when there is missing data. Regarding the weighted analyses, the treatment arm (gemcitabine + FOLFIRI.3) and the number of metastatic sites (one site) seemed to be independently associated with longer QFS of physical functioning [36]. The number of metastatic sites (more than one vs. one) were associated with a shorter QFS of GHS (global health status), fatigue and pain [36]. In multivariate analyses, treatment arm (gemcitabine + FOLFIRI.3) and number of metastatic sites (one site) tended to be associated with longer QFS of physical functioning in the weighted analysis [36]. In conclusion, analyses of QFS in this study demonstrated that FOLFIRI.3 and gemcitabine in patients in first line metastatic PDAC is feasible and, despite more toxicities, delayed the HrQoL deterioration [36]. Moreover, using the propensity score methods controlled for the imbalance of informative missing data between the two arms and provided more precise estimation of the true benefit of the treatment [36].

The NAPOLI-1 study was a global phase III, randomized, open-label, multicenter trial (NCT01494506) that tested liposomal irinotecan (nal-IRI; Onivyde®; MM-398) with or without 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) for patients with PDAC who had progressed following gemcitabine-based therapy [43]. The nal-IRI+5-FU/LV regimen led to significant improvements in median overall survival (OS; an increase by 45% [6.1 months vs. 4.2 months]; hazard ratio 0.67; 95% CI 0.49–0.92; $P = 0.01$]). This regimen also significantly improved a number of secondary endpoints, including progression-free survival [42]. A recently updated analysis confirmed this survival benefit. Side effects reported for the nal-IRI+5-FU/LV combination were manageable and typically reversible; the most frequent grade ≥3 adverse events included neutropenia, diarrhea, and vomiting [42]. HrQoL was a secondary endpoint in the NAPOLI-1 study. The EORTC QLQ-C30 was administered at baseline (within 7 days of starting treatment), every 6 weeks thereafter, and 30 days after discontinuation of study treatment, and a ten-point change in the EORTC QLQ-C30 was considered clinically meaningful [85, 88]. For global health subscales and functional subscales, patients were categorized as improved (≥10% improvement *vs.* baseline and remaining improved over baseline for ≥6 weeks), worsened (either died or had scores that worsened by 10% vs. baseline), or stable (did not meet criteria for improved or worsened). Duration of improvement was the interval between the first date when the score improved ≥10% and the date when the score returned to baseline or lower. This analysis shows that patients had no substantial deterioration from baseline in most HrQoL subscales [42]. The only differences from baseline between the nal-IRI+5-FU/LV combination and 5-FU/LV control therapy were a lower physical functioning score (−6.7) and a higher fatigue score (+11.1) with nal-IRI+5-FU/LV [42]. Patients subjectively assessed these changes as "minor" for physical function and "moderate" for fatigue [85]. In a post hoc analysis of the NAPOLI-1 study, using the quality-adjusted time without

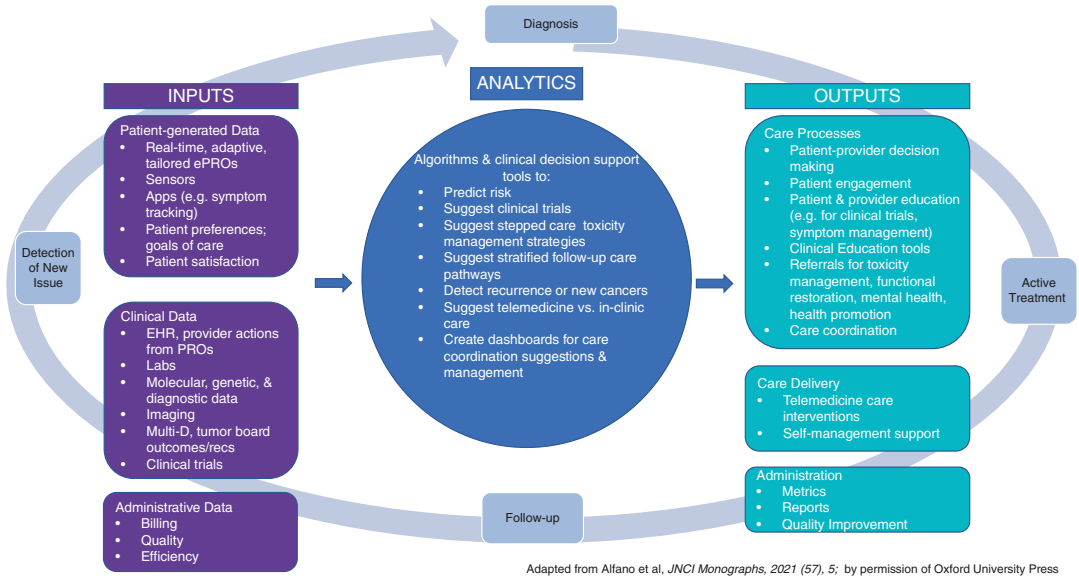
symptoms or toxicity (Q-TWiST) methodology, nal-IRI+5-FU/LV provided a relative gain of 24% compared with 5-FU/LV [89], exceeding the 15% difference threshold considered clinically meaningful [3].

The HrQoL findings from NAPOLI-1 are supported by Q-TWiST and complement previously reported survival benefit [42, 89], suggesting that nal-IRI+5-FU/LV also maintains HRQOL in patients whose disease has progressed on a prior gemcitabine-based regimen, despite the addition of an active chemotherapy agent. Generally, HrQoL assessments have seldom been reported in pancreatic cancer trials, both in first-line or second-line settings [19, 63, 87]. This may be because poorly controlled metastatic PDAC (mPDAC) has a high symptom burden. In the NAPOLI-1 trial, the EORTC QLQ-C30 questionnaire compliance rate was high until week 12 of treatment, after which the frequency of missing or incomplete data increased [42]. The vast majority of missing data were explained by terminal missingness, the most frequent reason being progressive disease [42]. This is consistent with other reports in mPDAC and reflects patient attrition typically observed in end-stage cancer studies [87, 90, 91]. As patients discontinued the study, EORTC QLQ-C30 compliance decreased. A more frequent HrQoL assessment may have increased data capture. It is unclear whether the improvements in HrQoL at week 12 were due to selection of patients with better HrQoL via attrition of patients with worsened QoL at week 6. It would be expected for this to be noted particularly with 5-FU/LV alone, as treatment discontinuation and progression were observed earlier in this arm [42]. Another reason could be general amelioration of side effects over time [91]. HRQOL improvements could also be due to adequate dose reductions and supportive measurements, improvement of disease symptoms via treatment of side effects, or a combination of all these factors. Other study limitations include a potential reporting bias because of the open-label design of the NAPOLI-1 study and a limited power to detect significant HrQoL differences between the two treatment arms. Additionally, the EORTC QLQ-C30 is a general questionnaire and may have failed to capture all nuances of mPDAC. Despite these limitations, this study provides randomized trial data on HrQoL, an important clinical insight.

Elderly and Poor Performance Status Patients

As described earlier, performance status is often a key factor in evaluating the appropriateness of therapy. It is a subjective composite measure used by clinicians to measure functional capacity and the likelihood of adverse events, QoL, and OS after treatment. Single agent systemic therapy such as gemcitabine in patients with advanced PS has historically been the favored approach although optimal treatment remains controversial in this setting due to lack of evidence [92]. Furthermore, there are no clear guidelines on how PDAC patients with poor PS such as ECOG 2 or worse or KPS of 70% or worse should be managed. However, clinical trials in metastatic patients with poorer PS who received multi-agent therapy with GnP had a greater reduction in the risk of death in comparison with GEM alone (79.3% vs. 90.7%) [93]. In a phase II trial of ECOG 2 patients, GnP was well tolerated and demonstrated acceptable efficacy [94]. Single-agent GEM + SBRT has also shown efficacy in non-metastatic PDAC with power performance status [21].

Similar to patients with poor PS, elderly patients are often excluded from clinical trials for PDAC. However, limited clinical trial data and several series have explored the potential benefits and downsides of surgical resection, chemotherapy, and radiation in the localized and metastatic settings [95]. The optimal treatment decision making remains challenging in these patients, but age should not be the primary determining factor for treatment decisions. A holistic approach to decision making would benefit these patients with consideration given to incorporating PRO and HrQoL measures for treatment selection.



Adapted from Alfano et al, *JNCI Monographs, 2021 (57), 5;* by permission of Oxford University Press

Fig. 28.4 Draft of technical requirements for a cancer data ecosystem inclusive of patient reported outcomes

Future Directions

Integrating PROs via patient online portals may increase PRO compliance, decrease missing data and correlate more reliably with clinical outcomes. Instead of simply monitoring QoL it may be helpful to include mind and body supportive services such as yoga and aerobic exercise. These services have been shown to improve QoL in breast cancer patients [96]. Moving forward, PDAC clinical trials should include PROs that encompass physical and social well-being (nutrition, pain and symptom management, family support), emotional and spiritual well-being (anxiety, depression, spirituality, etc.), advanced directives, and planning for the future throughout the entire trajectory of care [97]. An example framework for this approach at Northwell Health Cancer Institute is outlined in Fig. 28.4. Future trials should consider incorporating PRO questionnaires for patients and caregivers, predisposing risk factors, and family history, due to the evidence found in multiple studies emphasizing the importance of treatment satisfaction and logging daily progress (Table 28.1). While the patient QoL questionnaires target physical, mental, and emotional well-being, the other questionnaires are to learn about all other aspects of the treatment process: the impact on the caregiver, the overall treatment experience, and behavioral and genetic risk factors that may predispose an individual for PDAC.

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Integrative Medicine in Pancreatic Cancer

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Introduction

Research has shown an undeniable link between lifestyle factors, such as our emotional, physical, and nutritional health, and our ability to prevent, control, and survive cancer. This observation is a powerful indication that our daily living choices can be used as additional approaches alongside conventional medical care to prevent cancer in the first place and improve cancer outcomes and overall health. Research advances have improved our understanding of why dietary patterns, our response to stress, and level of physical activity may impact cancer progression and response to treatment. However, the current evidence is far from being adequate to set a complete and clear standard that can be followed by cancer patients to make lifestyle changes in a safe and effective way that is complementary to conventional oncologic treatments. At the same time, a vast amount of publications and misinformation including anecdotal stories are easily accessible to the general public via different media outlets, offering diverse interpretations of scientific findings and often conflicting advice on lifestyle modifications and alternative treatments. Cancer patients are motivated to make lifestyle changes that would improve their outcomes. They desire communication from their oncology team about making the right lifestyle choices and understanding the right complementary treatments that are beneficial to their overall cancer care. Providing evidence-based guidance is more important than ever. It is essential for cancer care professionals to have an open conversation about all forms of complementary therapies, albeit many unconventional, and provide guidance to cancer patients to prudently integrate lifestyle changes and complementary modalities alongside their conventional cancer care.

Integrative medicine seeks to combine conventional medicine with the safest and most effective complementary therapies. Although applying the concept of integrative medicine to cancer care is still relatively new, a number of comprehensive cancer centers in the USA are trying to put this concept into practice under the term of *integrative oncology*. As a result of growing interest in integrative oncology, the National Cancer Institute formed the Office of Cancer Complementary and Alternative Medicine, the American Cancer Society dedicated a portion of its website to assessment of complementary ther-

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© Springer Nature Switzerland AG 2022
M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3_29

apies, the Academic Consortium for Integrative Medicine and Health (ACIMH) formed an oncology working group, and the Society for Integrative Oncology (SIO) was formed. This chapter reviews the role of integrative medicine in cancer care with an emphasis on effective communication, an overview of the evidence, integrative-based resources to guide healthcare providers and patients, and an example of how to effectively incorporate integrative medicine within cancer care.

Definitions

Complementary and alternative medicine (CAM) has been defined by the National Center For Complementary and Integrative Health (NCCIH) and major US surveys as "diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine [1]." Although evidence may exist for some of these modalities, it may not be sufficient to bring them into the realm of conventional medicine, and other CAM modalities may have no support for their use. Alternative medicine is the use of a nonconventional treatment modality in place of conventional medicine whether or not there is evidence for its efficacy. Complementary medicine on the other hand, is making use of a non-conventional treatment modality in combination with conventional medicine whether or not evidence exists for its efficacy. Several different types of specialty healthcare providers offer CAM therapies and these may include physicians, nurses, physical therapists, psychologists, acupuncturist, and massage therapists who are operating within the guidelines of their licenses or accrediting organizations. Practitioners of all disciplines should be knowledgeable and aware of all treatment options and open to communication with other types of practitioners.

Integrative medicine seeks to merge conventional medicine and complementary therapies in a manner that is comprehensive, personalized, evidence-based, and safe. According to a published expert consensus statement definition from the Society for Integrative Oncology, integrative oncology is defined as a "patient centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during and beyond cancer treatment [2]." Integrative oncology is the application of integrative medicine to the care of patients with cancer and their caregivers [2].

Utilization

The World Health Organization (WHO) estimates that up to 80% of people in developing countries rely on nonconventional traditional medicines for their primary health care [3]. People in more developed countries also seek out complementary medicine and practices. A 2012 survey by the US Centers for Disease Control and Prevention found that 30% of adults had used CAM therapies at least once during the past 12 months [4]. Among patients and families touched by cancer, the use of CAM is higher than in the general population. An estimated 40–69% of US patients with cancer use CAM therapies and percentages increase if spiritual practices are included [5]. CAM therapies are used by up to 69% of cancer patients, with increased use in those with advanced cancers [5–7].

In most cases, people who use CAM are not disappointed or dissatisfied with conventional medicine but want to do everything possible to regain health and improve quality of life (QOL), reduce side effects, stimulate immunity, or prevent new cancers or recurrences [5, 8]. Whether or not patients use CAM therapies to treat cancer or its side effects, they may use them to treat other chronic conditions such as arthritis, heart disease, diabetes, and chronic pain [8].

Communication

Research indicates that neither adult nor pediatric patients receive sufficient information or discuss CAM therapies with physicians, pharmacists, nurses, or CAM practitioners [9, 10]. It is estimated that 42% of patients with cancer are taking complementary medicines without informing any member of their healthcare team, mostly due to physician not asking about CAM use [10]. Patients may believe that it is unimportant for their physicians to know about their CAM use [10]. This lack of discussion is of concern because herbs and supplements may have contribute to toxicity or interact with cancer treatments. There were 9854 known reported cases of adverse herbal-drug reactions in 2002 alone in China, nearly double the number reported in 10 years between 1990 and 1999 [11]. Patients are commonly unaware of the differences between the United States Food and Drug Administration (FDA) approved medications (which require evidence of efficacy, safety, and a quality control manufacturing) and supplements, which are governed not by FDA but by the Dietary Supplement Health and Education Act (DSHEA) of 1994. Supplements under this legislation are exempt from the same scrutiny the FDA imposes on medications; furthermore, these supplements are not intended to treat, prevent, or cure diseases. The common belief by patients that "natural" means safe needs to be addressed with education as some herbs and supplements have been associated with multiple drug interactions, as well as increased cancer risks and organ toxicity [12]. However, nearly four in 10 Americans believe that "alternative treatments" may cure cancer according to the American Society of Clinical Oncology (ASCO)'s second annual National Cancer Opinion Survey in 2018 [13]. One-fifth of patients with cancer believed that their disease could be cured solely through alternative therapies. Empathetic communication strategy and inquiring why patients are seeking these therapies may uncover unmet needs of the patient including emotional support.

Existing research suggests that the majority of cancer patients desire communication with their physicians about CAM [14]. There is general agreement within the oncology community that in order to provide optimal patient care, oncologists must not only be aware of CAM use but also be willing and able to discuss all therapeutic approaches with their patients. It is the healthcare professional's responsibility to ask patients about their use of complementary medicines, and the discussion should ideally take place before the patient starts using a complementary treatment–whether it is a nutritional supplement, mind-body therapy, or other CAM approach.

A number of strategies can be used to increase the chance of a worthwhile dialogue. One approach is to include the topic of CAM as part of a new patient assessment. For example, when asking about medications, physicians should inquire about everything the patient ingests–including over-the-counter products, vitamins, minerals, herbs, and the patient's diet. Physicians may consider having the patient bring in the actual bottles of herbs and supplements for evaluation. When asking about a patient's past medical history, physicians should ask about all other healthcare professionals involved in the patient's care, including encounters with CAM practitioners such as naturopaths or chiropractors. If the issue of CAM arises, clinicians need to develop an empathic communication strategy that addresses the patient's needs while maintaining an understanding of the current states of the science [15]. The strategy needs to be balanced between clinical objectivity and bonding with the patient so that it can benefit both the patient and the health care provider. The physician who is receptive to patient inquiries is able to establish an environment in which the patient feels comfortable to bring up the topic of CAM therapies. Part of this strategy should be an open attitude combined with a willingness to review evidence-based references and consult with other healthcare professionals. Patients need reliable information on CAM from reliable

resources, as well as adequate time to discuss this information with their oncologists [16].

The Evidence

The field of integrative oncology is a constantly evolving set of disciplines. In the following section, we review key areas where there is sufficient evidence to recommend the therapies: mind-body practices, massage, and acupuncture. Although there is ongoing research in many other areas such as healing touch, homeopathy, natural products, and special diets, there is insufficient evidence to recommend these at this point in time. Evidence on nutrition in cancer patients as well as nutritional approaches to pancreatic cancer and treatment related metabolic and digestive disturbances is discussed in a separate Nutrition chapter.

Supplements

An extensive collection of epidemiological studies have testified to the importance of nutrition in human cancer development [17, 18]. For example, a diet that is low in cereals, vegetables, and fruits, but high in meat is associated with increased risk for colorectal cancer. Nutrient deficiencies leading to biochemical disturbances could be one of the mechanisms by which certain dietary patterns promote neoplastic processes [19]. The concept of using dietary chemicals for cancer prevention has been explored in both mechanistic laboratory studies and human trials. Though the rationale of chemoprevention of cancer with dietary nutrients seems plausible from ample epidemiological and laboratory evidence, no single or combination of dietary supplements have been shown to be useful for cancer prevention. In fact, many vitamin supplements may have harmful effects on health, including increasing cancer risks [20] [21].

Early epidemiologic studies observed an inverse correlation of human cancer risks with blood retinol level and dietary beta-carotene intake [22]. Unexpectedly, in a multicenter, randomized, controlled prevention trial involving 18,314 smokers, former smokers, and workers exposed to asbestos in the USA, the group treated with beta-carotene supplements had increased risk for lung cancer by 28% compared with the placebo group [20]. The selenium and vitamin E cancer prevention trial (SELECT) was a prospective randomized trial examining the effect of these two agents for prostate cancer prevention. Contrary to a hypothesized benefit based on preclinical and epidemiologic evidence, compared to those who had taken a placebo, the men who had taken vitamin E had a 17% increased risk of developing prostate cancer [21].

Vitamin B 12 and/or vitamin B complex are often taken to help reduce fatigue and improve energy. But recent evidence reveals that supplementation with B-vitamins is associated with a higher risk of colorectal cancer (HR 1.77; 95%CI 1.08–2.90, $p = 0.02$) as well as overall cancer (HR 1.25; 95%CI 1.00–1.53, $p = 0.05$) [23]. The association between vitamin B6 and B12 and lung cancer risk is even more striking. The lung cancer risk almost doubled among men taking vitamin B6 (>20 mg/d; HR, 1.82; 95% CI, 1.25 to 2.65) and B12 (>55 μg/d; HR, 1.98; 95% CI, 1.32 to 2.97) compared with nonusers [24], with even greater risk among men who were smoking at baseline.

Vitamin E, an antioxidant, if adequately obtained from foods, may lower risk for nonsmoking women, especially those exposed to secondhand smoke [4]. However, vitamin E supplements may increase lung cancer risk in these groups.

The incidence of vitamin D deficiency/insufficiency is higher among patients with cancer than those without [25]. An inverse correlation has been observed between risk for prostate cancer and sun exposure and serum vitamin D levels [26, 27]. In the setting of colorectal neoplasia, taking vitamin D and/or calcium supplements does not reduce the risk of colorectal adenoma recurrence [28].

Human trials with vitamin supplements often do not support the findings of the epidemiologic studies. One important lesson we have learned from these disappointing results is that constitu-

ents derived from foods most likely do not exert the entire nutritional effects of the whole foods, and they may not work alone to defend us from diseases. Though vitamin C is a strong antioxidant, a whole fresh "Red Delicious" apple with skin has an antioxidant activity equivalent to the amount of vitamin C from 260 apples [29]. Many epidemiologic studies used nutrients as markers to estimate intake levels of certain foods. With the understanding that our nutritional knowledge is still insufficient and fragmentary, we need to take considerable caution to avoid over interpreting observational data and rush nutrient supplements to human trials or even clinical use.

One of the frequent referrals to our Integrative Medicine Clinic is for guidance on supplements/vitamins/herbs during cancer treatment. Patients with cancer often take antioxidant supplements, hoping to improve cancer control and prevent cancer therapy related side effects. High-quality clinical evidence is often not readily available to help oncology providers guide cancer patients about the safety and efficacy of their supplement use during active chemotherapy and/or radiation treatment. There have been opposing views about the use of antioxidant during active cancer therapy. On one side, supplementation with natural compound including antioxidants is rationalized to enhance cancer response to chemotherapy, reduce or prevent side effects, and improve quality of life [30]. However, on the other hand, antioxidants are recommended against because they may protect tumor cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapeutic agents [31]. In a randomized and placebo-controlled study involving 540 head and neck cancer patients receiving radiation therapy, those who received antioxidants (alfa-tocopherol alone and beta-carotene), though having fewer severe acute side effects [32], had significantly higher rate of recurrence or second primary cancer [33] as well as poorer overall survival [34]. Subgroup analysis of the same cohort revealed that concurrent antioxidant supplementation and cigarette smoking during radiation therapy were associated with an increase in both disease recurrence and caner-specific mortality [34], In another study involving 1134 breast cancer patients receiving chemotherapy with cyclophosphamide, doxorubicin, and paclitaxel, use of any antioxidant supplement (vitamins A, C, and E; carotenoids; coenzyme Q10) both before and during treatment was associated with an increased hazard of recurrence [35]. In addition, vitamin B12 use both before and during chemotherapy was significantly associated with poorer disease-free survival and overall survival. Use of iron during chemotherapy was significantly associated with recurrence [35].

While concurrent use of vitamin/antioxidant supplementation during radiation or chemotherapy poses potential harm [31], there has been no evidence to suggest that antioxidant nutrients obtained in usual dietary amount from fruits and vegetables has deleterious effects on human health. Dietary supplements accounts for an estimated 23,000 US emergency room visits every year, with cardiovascular side effects related to supplements for weight loss or energy products leading to the most visits [36]. American Cancer Society (ACS) and American Institute for Cancer Research (AICR) strongly recommend general population and cancer survivors to obtain nutrients through foods rather than supplements [37, 38].

There is a lack of evidence about benefit and harm of use of other natural products in cancer patients, such as herbal extracts. Herb–drug interactions are of major concern. As an example, St. John's Wort, which is often used by patients for mood disorders, may interfere with liver metabolism of Sunitinib, Sorafenib, and Everolimus [39]. Similar herb-drug interaction exists with herbal teas of chamomile and peppermint [39]. Valerian, a supplement used to aid sleep, was reported to interfere with liver metabolism and contribute to liver toxicity [40]. For patients and clinicians who seek objective data on potential safety, mechanism of natural products or herbal–drug interactions, Natural Medicines (https://naturalmedicines.therapeuticresearch.com/) and the "About Herbs" website of the Memorial Sloan-Kettering Cancer Center can be a resource to evaluate the potential benefit and harm of herbal use in the oncology setting [41].

Mind-Body Practices

The belief that what we think and feel can influence our health and healing dates back thousands of years. The importance of the role of the mind, emotions, and behaviors in health and well-being is central to traditional Chinese, Tibetan, Greek, and Ayurvedic medicines and other medical traditions of the world.

The health damaging effects of chronic stress are well documented in the medical literature. Research shows that chronic stress affects almost every biological process in our bodies [42]. Unmanaged chronic stress can speed the aging process through telomere shortening [43], increasing the risk for cardiovascular diseases [44], sleeping difficulties [45], digestive problems [46], and even depression [47, 48]. Research has also shown that stress can also decrease compliance with health-screening behaviors and treatment [49]. Moreover, it can also cause patients to forego healthy eating and exercise habits that help prevent cancer and other disease.

With regard to cancer, there is little convincing evidence that chronic stress affects cancer initiation; however, there is extensive evidence that chronic stress can promote cancer growth and progression [50, 51]. The underlying mechanism for such effects are complex and involve chronic activation of the sympathetic nervous system and the = hypothalamic-pituitary-adrenal axis [52]. Sustained elevations from these pathways (e.g., norepinephrine and cortisol) result in diverse effects including stimulation of cancer invasion, angiogenesis, inflammation and immune dysregulation, reduced anoikis, and even reduced efficacy of chemotherapy drugs [53].

The clinical significance of stress-induced biological changes and the changes in the tumor micro-environment has not been widely studied. However, these changes may be significant enough to affect not only the immediate health of the patient but also the course of the disease and thus the future health of the patient. It is, therefore, prudent to suggest that patients engage in some type of mind-body practice to reduce stress in their lives.

Mind-body practices are defined as a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Mind-body techniques include relaxation, hypnosis, visual imagery, meditation, biofeedback, yoga, tai chi, Qi Gong, and other movement-based therapies, cognitive behavioral therapies, group support, autogenic training, and spirituality as well as expressive arts therapies such as art, music, or dance. As research continues, the treatments that are found beneficial will hopefully become integrated into conventional medical care.

Techniques of stress management that have proven helpful include progressive muscle relaxation, diaphragmatic breathing, guided imagery, and social support. Participating in stress management programs before treatment has enabled patients to tolerate therapy with fewer reported side effects. Supportive expressive group therapy has also been found to be useful for patients with cancer. Although there is some data to support the use of expressive art therapies such as music therapy [54, 55], art therapy [56, 57], and expressive writing [58] and journaling to improve QOL, the number of trials is limited and they typically have a small sample sizes and often no control groups. Psychosocial interventions have been shown to specially reduce anxiety, depression, and mood disturbances in cancer patients and assist their coping skills [59].

Newell et al. [60] reviewed psychosocial therapies for cancer patients and concluded that interventions involving self-practice and hypnosis for managing nausea and vomiting could be recommended. Ernst et al. [61] examined the change in the state of the evidence for mind-body therapies for various medical conditions between 2000 and 2005 and found that there is now maximal evidence for the use of relaxation techniques for anxiety, hypertension, insomnia, and nausea due to chemotherapy. The beneficial effects of hypnosis, and specially self-hypnosis, is further supported by more recent research as hypnosis was found beneficial for reducing distress and discomfort during difficult medical procedures [62, 63]. An NIH Technology Assessment Panel found strong evidence for hypnosis in alleviating

cancer related pain [64]. Hypnosis effectively treats anticipatory nausea in pediatric and adult cancer patients, reduces postoperative nausea and vomiting, and improves adjustment to invasive medical procedures, and when combined with cognitive behavioral therapy (CBT), hypnosis leads to reduced fatigue in women with breast cancer at the end of radiation therapy and 1 and 6 months later [65].

Research examining yoga, tai chi, and meditation, including mindfulness-based stress reduction (MBSR), incorporated into cancer care suggests that these mind-body practices help to improve aspects of QOL including improved mood, sleep quality, physical functioning, and overall well-being of patients undergoing treatment and cancer survivors [66].

The meditation practice that has been researched the most is MBSR. The larger randomized controlled trials (RCTs) of meditation published in the past few years have used some form of MBSR for women with breast cancer. MBSR has been found to reduce self-reported levels of anxiety and depression and improve sleep quality; it has reduced the long-term emotional and physical adverse effects of medical treatments, including endocrine treatments; and resulted in a significant reduction in mood disturbance and symptoms of stress. A cancer-specific version of MBSR called mindfulness-based cancer recovery (MBCR) found that breast cancer survivors scoring 4 or greater in the distress thermometer had lower symptoms of stress and improved QOL [67]. In addition, both MBCR and a supportive expressive therapy group resulted in more normative diurnal cortisol profiles than a control group. According to the (2019) National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, meditation, and mindfulness strategies can help provide relief for cancer patients experiencing distress and pain and other behavioral strategies like relaxation and hypnosis can reduce nausea. According to the recent (2018) joint Society for Integrative Oncology (SIO) and American Society of Clinical Oncology (ASCO) clinical practice guidelines for use of integrative therapies during and after breast cancer treatment, meditation is recommended for reducing anxiety, treating mood disturbance and depressive symptoms, and improving quality of life (Grade A evidence) [68].

The more movement-based mind-body practices such as yoga, and tai chi/qi gong typically combine physical postures or movements, breathing techniques, and meditation with the goal to enhance health and well-being. Several systematic reviews and meta-analysis indicate QOL benefits associated with practicing yoga in cancer patients and survivors [69, 70]. Research demonstrates that yoga is useful for treating sleep disturbances [71] and fatigue [72]. Yoga has also been found to reduce inflammatory signaling and stress hormone regulation [73], which plays a role in behavioral symptoms such as fatigue after breast cancer treatment [73, 74]. Thus, yoga may actually impact biological pathways beyond patient's perceptions of QOL and symptoms. Although most yoga research has been conducted in women with early-stage breast cancer, efforts are underway to extend these findings to women with advanced breast cancer and survivors of lung cancer and caregivers [75]. According to the (2018) joint Society for Integrative Oncology (SIO) and American Society of Clinical Oncology clinical practice guidelines for use of integrative therapies during and after breast cancer treatment, yoga is recommended for reducing anxiety, improving quality of life, mood and depressive symptoms (Grade B), and for improving fatigue and sleep (Grade C evidence). Similarly, the 2019 NCCN guidelines recommends yoga as an effective intervention for anticipatory nausea/vomiting and cancer related fatigue. For patients and caregivers, our own research suggests that yoga can lead to improvements in mental health aspects of quality of life, sleep disturbances, physical functioning, finding meaning in the illness experience, and stress hormone regulation [76, 77].

Studies have shown that tai chi can improve physical performance in the areas of strength, flexibility, balance, and respiratory function [78, 79]. In a meta-analysis by Zeng et al., tai chi/qi gong had positive effects on cancer-specific quality of life, sleep quality, and fatigue and stress in

cancer patients [80]. A systematic review and meta-analysis of studies in the cancer care setting found that tai chi/qi gong were associated with significant improvement in fatigue, sleep difficulty, depression, and overall quality of life [81]. Another recent systematic review of 22 randomized controlled trials of tai chi in cancer survivors, identified moderate-level evidence for improvements in cancer related fatigue, reduction in cortisol levels, and positive effects on upper limb function and muscle strength [82]. In a study of Tai Chi Chih (a manualized form of tai chi) compared with cognitive behavioral therapy for insomnia in breast cancer survivors, both interventions contributed to clinically significant reductions in insomnia [83].

According to the (2018) joint Society for Integrative Oncology (SIO) and American Society of Clinical Oncology clinical practice guidelines for use of integrative therapies during and after breast cancer treatment, qi gong can be considered for improving quality of life (Grade C) [68].

Mind-body practitioners with experience in cancer patient populations can provide guidance to help patients engage safely in practices such as meditation, yoga, tai chi, and qigong. Mind-body approaches should be considered as adjunctive approaches to help with poor mood, anxiety, insomnia, fatigue, pain, nausea, and overall QOL together with conventional therapies such as psychotherapy, cognitive behavioral therapy, and pharmacological approaches.

Massage

Massage has shown promise for relief of cancer and cancer treatment-related symptoms. As a manipulative touch-based therapy, massage can benefit cancer patients when performed by therapists who have an awareness of the special-needs of cancer patients [84]. A massage therapist with special training in oncology massage is the best equipped to safely deliver the therapy. Risk of bruising, bleeding, or injury can be minimized by careful application of pressure, avoiding massage into the deep tissue or bone in selected patients. Areas that have recently had surgery or radiation should be avoided. In patients with extremities subjected to lymphedema, therapist will need to adjust their technique to maximize safety. Patients may benefit from formal lymphedema therapy as part of a physical therapy program [85].

Research suggests that massage is helpful at relieving pain, anxiety, fatigue, distress, and increasing relaxation [86, 87]. Benefit of mood and pain relief is limited to the more immediate effort of massage, with no concurrent studies demonstrating long-term relief [88, 89]. Anecdotal and case report evidence suggested benefit of massage for the relief of chemotherapy-induced peripheral neuropathy. A massage to the feet, hands, and head can provide therapeutic benefit as these areas are especially sensitive to tactile stimulation and can result in relaxation and increased well-being. Massage provided by caregivers may offer a unique opportunity for interaction between patient and caregiver that can help enhance the well-being of both [90]. In addition to symptomatic relief, studies have also demonstrated systemic effects of massage, with the decreases in cortisol levels resulting from a massage intervention [91]. More research is needed to better understand massage mechanisms and treatment protocols (ideal massage type, dosing) to better define the role of massage therapy in cancer symptom management.

Acupuncture

Acupuncture is a treatment modality that is part of traditional Chinese medicine (TCM). It has been practiced in China for thousands of years and is used in at least 103 countries throughout the world [92]. According to TCM theory, the placement of acupuncture needles, heat, or pressure at specific body points can help regulate the flow of Qi (vital energy) within the body. The most common form of acupuncture involves the placement of solid, sterile, stainless steel needles into various sites on the body that are believed to have reduced bioelectrical resistance and increased conductance. The needles may be stim-

ulated manually or a mild electrical current may be applied directly to the needles after insertion. Stainless steel or gold (semi-permanent) needles, or "stats," are also sometimes placed at points on the ears and left in place for 3–5 days.

The strongest evidence supporting the use of acupuncture in cancer care is for symptom management. Studies have shown that acupuncture is helpful to control nausea and vomiting from multiple causes [i.e., chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting, and pregnancy] [93, 94], and although there is good evidence for the use of acupuncture to control pain, there is still limited research in a cancer setting. In a large individual patient-level data meta-analysis of 29 trials involving noncancer patients (N = 14,597) with chronic pain, significantly better pain control was found in favor of real acupuncture compared to no acupuncture as well as real acupuncture compared to sham acupuncture, though to a lesser degree [95].

For the management of other treatment or cancer related symptoms, the evidence is not as strong as that for pain and nausea; however, initial research suggests that acupuncture may help reduce the severity of radiation-induced xerostomia with a lasting benefit [96, 97]. Additionally, some evidence supports the benefit of acupuncture for management of constipation, loss of appetite, peripheral neuropathy, hot flashes, fatigue, insomnia and sleep disorders, dyspnea, anxiety/depression, and leukopenia [98]. In recent years, high quality acupuncture clinical trials further strengthen the evidence base of acupuncture for oncology practice. Hershman et al. recently found that acupuncture was more efficacious that sham control and usual care for arthralgia related to aromatase inhibitor related arthralgia [99]. Mao et al. found that acupuncture had similar effect as gabapentin for management of hot flashes but with fewer side effects; in addition, the effects of acupuncture was more durable than gabapentin [100]. Garland et al. found that acupuncture produced clinical meaningful and durable treatment effects for insomnia, particularly for patients with insomnia comorbid with pain [101]. Lastly, in a large multi-center trial, Garcia, Cohen, and colleagues found that acupuncture reduced the severity of xerostomia (dry mouth) in over 300 cancer patients with head and neck cancer undergoing radiotherapy, with the effects lasting for up to 12 months after the end of radiotherapy [102].

With the growing evidence base and desire to meet patient needs, many comprehensive cancer centers incorporate acupuncture for cancer symptom management [103] with almost all cancer centers recommending acupuncture for symptom management [104]. Our own published experience in an outpatient cancer care setting has demonstrated statistically and clinically significant effects of acupuncture on self-reported symptoms [105]. The NCCN guidelines list acupuncture as an effective strategy for managing nausea and pain. More recently, CMS has approved the use of acupuncture for the treatment of back pain.

When performed correctly, acupuncture has been shown to be a safe, minimally invasive procedure with very few side effects. The reported side effects include fainting, bruising, and mild discomfort. Infection is a potential risk, but very uncommon when treatment is provided by a qualified acupuncturist. Treatments should only be performed by a healthcare professional with an appropriate license and experience.

Educational Resources

Comprehensive reviews can quickly become outdated, and the ease of Internet publishing has fostered the growth of comprehensive scientific review organizations that provided electronic access to their reviews. We outline websites of organizations providing reliable information for providers and patients (Table 29.1).

The American Cancer Society (ACS) and the National Cancer Institute (NCI) Office of Cancer Complementary and Alternative Medicine (OCCAM) provide valuable educational resources for patients and the general public on complementary therapies. Natural Medicines Comprehensive Database provides evidence based reviews of complementary therapies. The Cochrane Review Organization, founded in 1993 as an international nonprofit independent organi-

Table 29.1 Recommended Internet resources for integrative oncology

Cochrane Review Organization	www.cochrane.org
ConsumerLab	www.consumerlab.com
Memorial Sloan Kettering Cancer Center	www.mskcc.org/cancer-care/treatments/symptom-management/integrativemedicine/herbs
University of Texas MD Anderson Cancer Center, Integrative Medicine Program	www.mdanderson.org/integrativemedcenter
Natural Medicines Comprehensive Database	www.naturaldatabase.com
National Center for Complementary and Integrative Health	www.nccih.nih.gov
National Cancer Institute Office of Cancer Complementary and Alternative Medicine	http://cam.cancer.gov
American Institute for Cancer Research	www.aicr.org
Society for Integrative Oncology	www.integrativeonc.org
American Cancer Society	https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/complementary-and-alternative-methods-and-cancer/using-cam-safely.html
National Cancer Institute	https://www.cancer.gov/publications/pdq

zation, provides systematic reviews that include complementary therapies.

Natural standard is part of a multidisciplinary, multi-institutional initiative dedicated to the review of complementary and alternative therapies. It follows a similar process to build in-depth evidence and consensus-based analysis of scientific data in addition to historic and folkloric perspectives. The integrative medicine service at the Memorial Sloan-Kettering Cancer Center provides evidence-based reviews as part of their "About herbs, Botanicals & Other Products" internet resource. The Integrative Medicine Program/Center website at the University of Texas MD Anderson Cancer Center serves as a resource for patients and providers interested in learning about the evidence-based role of integrative medicine in cancer care.

Integrative Oncology in Clinical Practice

Integrative oncology can improve cancer outcomes by incorporating additional treatment options that contribute to improved health, symptom management, and QOL. Most major medical centers now offer some complementary medicine treatment modalities alongside conventional care. In order to deliver comprehensive integrative cancer care, complementary therapies must be part of an evidence-informed, personalized, coordinated care plan that synergizes with ongoing conventional cancer therapies.

The Integrative Medicine Center at MD Anderson Cancer Center is a leading example of integrative oncology in clinical practice. The center utilizes a biopsychosocial model of healthcare (Fig. 29.1) as a clinical framework to guide education and delivery of services to patients and their caregivers. Physician directed clinical services are provided to address symptom control needs such as pain or anxiety or education regarding herbs and supplements. The Center provides patient care on an individual bases as well as in groups. Patients may receive inpatient and outpatient physician consultation, acupuncture, massage, and mind-body therapies such as meditation, yoga, and music therapy. Physical therapy for exercise counseling, a dietitian for nutrition counseling, and health psychologists for mood management and behavioral counseling are also

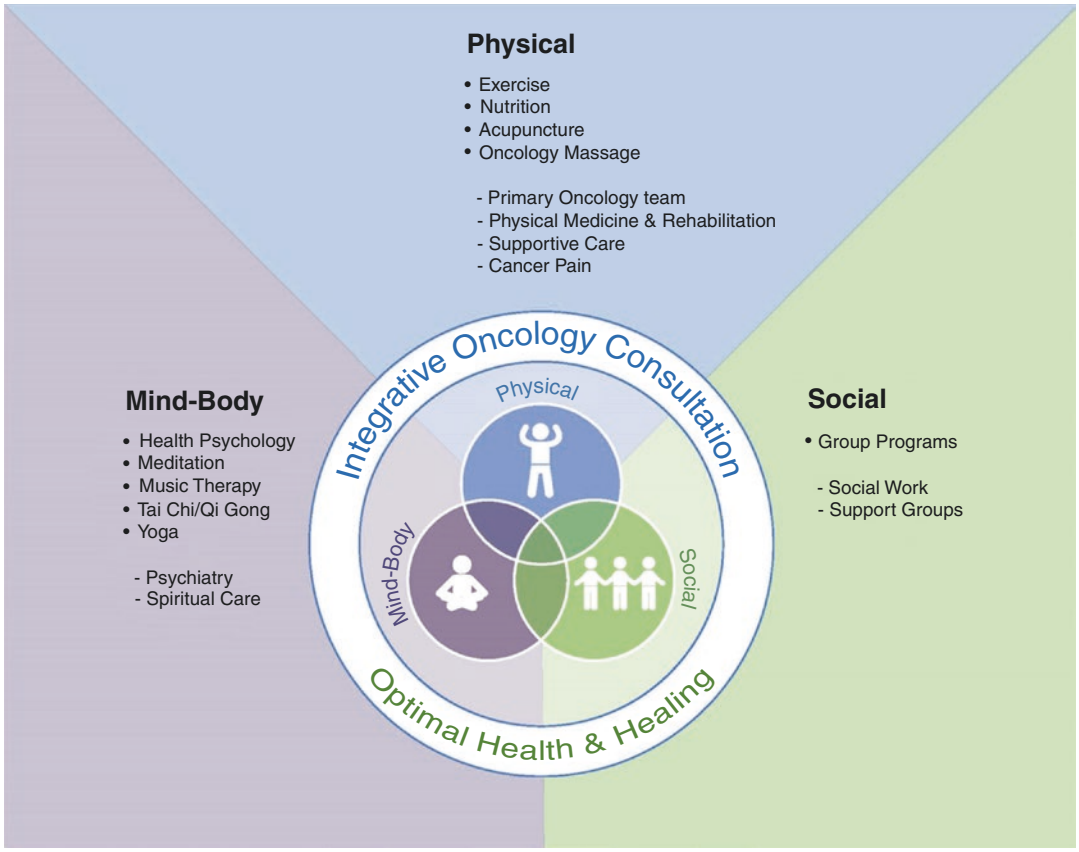

Fig. 29.1 Biopsychosocial model of healthcare

available for all patients. Patients can also attend free group classes such as meditation, yoga, tai chi/qi gong, music therapy, exercise, and cooking classes. All staff members meet on a weekly basis to discuss challenging new patients and to help coordinate care. Clinical encounters are documented in the electronic health record. As part of routine care, patients complete validated instruments on symptoms and QOL and are included as part of a broader clinical research initiative to understand clinical impact of the integrative services provided. The Integrative Medicine Center works collaboratively with other supportive services such as palliative medicine, psychiatry, pain center, and rehabilitation services. Referrals come from these service areas as well as from primary oncology teams or the cancer prevention center.

Conclusion

Integrative oncology is a rapidly expanding discipline that holds tremendous promise for additional treatment options and more effective symptom control. Organizations such as NCCN, ASCO, and SIO have published guidelines that support the use of integrative medicine during and after cancer treatment. An integrative approach provides patients with a more personalized system of care to meet their needs. The majority of patients either are using complementary medicines or want to know about them, so it is incumbent on the conventional medical system to provide appropriate education and clinical services. The clinical model for integrative care requires a patient-centered approach with attention to patient concerns and enhanced communi-

cation skills. In addition, it is essential that conventional and nonconventional practitioners work together in developing an integrative model. In this way, cancer patients will be receiving the best medical care making use of all appropriate treatment modalities.

Acknowledgements We thank Alejandro Chaoul, Richard Tsong Lee, Mary Kay Garcia, and Moshe Frenkel for their input on a previous version of this chapter.

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M. S. Bhutani et al. (eds.), *Pancreatic Cancer: A Multidisciplinary Approach*,
https://doi.org/10.1007/978-3-031-05724-3