Pancreatic Cancer

16

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16.1 Introduction

The incidence of pancreatic cancer is on the rise [1, 2]. Surgery has traditionally been considered the cornerstone in the management of resectable pancreatic cancer [3, 4]. However, we now know that improved outcomes can be achieved by combining surgery with chemotherapy under the broad umbrella of multimodality therapy [5, 6]. This multimodality approach is best suited to only 20% of patients with pancreatic cancer who present when the disease is still amenable to surgical resection. The vast majority of patients, though, present with advanced disease where the aim of therapy is disease control through efforts directed at retarding its progression [7–9].

While surgical resection rates, as well as adjuvant and palliative chemotherapy rates, have increased in the last couple of decades, there has not been a corresponding improvement in overall survival [10]. The more concerning statistic is the steadily rising mortality associated with this cancer which is unlike any other organ subsite [1, 11–14].

All this points to the fact that there yet remains much to be learnt about the biology of pancreatic cancer [15]. However, instead of the oft-adopted nihilistic view towards this cancer, we need to focus on the strategies that have provided us some success in combating the illness. This chapter provides a concise, evidence-based perspective on pancreatic cancer with an aim to highlight what is known about it and how we, as clinicians, can positively impact the outcome of these patients. Potential areas for further research are highlighted.

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16.2 Epidemiology

Pancreatic cancer accounted for 338,000 new cases in the year 2012, making it the 12th most common cancer worldwide (2.4% of all cancers excluding non-melanoma skin cancer) [16]. Keeping up to its deadly reputation, it ranks amongst the top four causes of cancer-related deaths worldwide [12, 14, 17].

The age-standardized incidence rates are varied across the world ranging from as low as 0.6/100,000 persons per year in parts of Asia to as high as 12.6/100,000 in the West [18]. However, even within regions, ethnic/racial variations do exist. In the United States, African Americans have a higher incidence of pancreatic cancer followed by Hispanics compared to other races (Caucasians and Asians). Patients of African American descent tend to present with a more advanced disease [19] and a worse overall survival [20]—a trend that has not significantly changed over the last three decades [21, 22]. There is some evidence to suggest an increased risk of pancreatic cancer amongst the Jews of North America [23].

In New Zealand, the Maoris have a higher incidence of the disease (7.3/100,000 persons per year) when compared to other ethnic groups. Interestingly, unlike the demographic profile of a male predominance that so characteristically represents pancreatic cancer [24], Maori women have an unusually high rate of the cancer (7.2/100,000) [25].

Pancreatic cancer generally presents at an older age (sixth to seventh decade of life) [24, 26]. Pancreatic cancer may occur rather uncommonly in younger patients. These individuals tend to be diagnosed at a more advanced stage, although the overall impact on survival remains unclear with one study from Japan [27] indicating a poorer survival while another European study demonstrated comparable survival to older counterparts [28]. However, there is no evidence to support a role for a genetic or hereditary causative component in these patients [27, 28].

16.2.1 Factors Implicated in the Pathogenesis of Pancreatic Cancer

16.2.1.1 Hereditary Pancreatic Cancer

At the outset it is important to appreciate the specific terminologies used in hereditary pancreatic cancer. The term hereditary pancreatic cancer encompasses two major subsets of patients with a significant family history of pancreatic cancer (≥2 relatives with pancreatic cancer if at least 1 is a first-degree relative or ≥3 total relatives with pancreatic cancer [29]). Patients with identified (known) genetic mutations are generally included under specific syndromes, while the term ‘familial pancreatic cancer’ is reserved for those families with ≥2 individuals who are first-degree relatives of one another with pancreatic cancer, in the absence of an identifiable genetic mutation [29].

Familial or genetic causes account for 10% of the overall cases of pancreatic cancer with a reliably high sensitivity of self-reporting [30]. Patients with hereditary pancreatic cancer tend to present 5 years earlier than the average median age at

diagnosis (66 vs 71 years) based on the findings of the Pancreatic Cancer Genetic Epidemiology Consortium [31].

Table 16.1 provides an overview of the various hereditary pancreatic cancer predisposition syndromes [32–41].

Patients with APC gene mutations (familial adenomatous polyposis) have an increased risk of ampullary and duodenal cancers.

Table 16.1 Hereditary pancreatic cancer predisposition syndromes

Syndrome	Phenotype	Organs at risk other than pancreas	Genetic mutations	Relative risk of pancreatic cancer compared to the general population	References
Peutz-Jeghers syndrome	Mucocutaneous pigmentation Hamartomatous polyps	Colorectal Breast Lung Uterus Testes	STK11	132	[32, 33]
Hereditary pancreatitis	Autosomal dominant inherited pancreatitis manifested as recurrent acute pancreatitis by age 10, chronic pancreatitis by age 20 and increased risk of PC after age 40	–	PRSS1	58	[34–37]
Familial atypical mole melanoma syndrome (FAMMM)	Early-onset multiple melanomas	Melanoma	CDKN2A	38	[32, 38]
Hereditary non-polyposis colorectal cancer (HNPCC)	Colorectal polyps	Colorectal Uterus Ovary Stomach Small intestine Urinary tract Biliary tree	MSH2, MLH1, MSH6, PMS2, 5′ EPCAM deletion	8.6	[32, 39]
Hereditary breast-ovarian cancer (HBOC)	Early-onset breast cancer	Breast Ovary	BRCA1 BRCA2	2.3 3.51	[40, 41]

PRSS1 protease, serine 1, *STK* serine/threonine kinase, *BRCA* breast cancer susceptibility, *CDKN2A* cyclin-dependent kinase inhibitor 2A, *MSH* MutS protein homolog, *MLH* MutL homolog, *PMS* protein homolog, *EPCAM* epithelial cellular adhesion molecule

Other mutations associated with hereditary pancreatic cancer but in whom the risk of disease development has not yet been clearly elucidated include PALB2 (additional risk of breast cancer) [42], monoallelic ATM (ataxia telangiectasia—individuals also at risk for developing breast and colon cancer) [43] and TP53 (Li-Fraumeni syndrome—individuals also at risk for developing breast, brain, sarcoma, adrenocortical and colon cancer) [44].

Patients with a strong family history of pancreatic cancer, hereditary pancreatitis or a known hereditary cancer syndrome must be advised germline genetic testing [29].

16.2.1.2 Sporadic Pancreatic Cancer

Several environmental factors have been implicated in the causation of pancreatic cancer. These factors are believed to play a significant role in the 90% of patients who do not possess a hereditary predisposition [45]. Table 16.2 provides an overview of these factors [28, 46–65].

Other risk factors include bacterial infections (*Helicobacter pylori* and a pathogen for periodontal disease, *Porphyromonas gingivalis*) [66], pancreatic cystic neoplasia (intraductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasia (MCN); see Chap. 12) [67] and pancreatic intraepithelial neoplasia (PanIN) [68].

There is evidence to suggest that vitamin D levels are a risk factor in the development of pancreatic cancer. However, to date, the epidemiological data is inconclusive [69].

16.3 Pathology

Infiltrating ductal adenocarcinoma is the most common type of pancreatic cancer on histopathology. The less common variants include adenosquamous carcinoma, colloid carcinoma, hepatoid carcinoma, medullary carcinoma, signet ring cell carcinoma and undifferentiated carcinoma (with or without osteoclast-like giant cells) [70]. Light microscopic features consistent with invasive cancer on haematoxylin and eosin staining include haphazard glandular growth pattern with glands adjacent to vessels or touching fat, incomplete glands, perineural and intravascular invasion, nuclear variation more than 4:1 and intraluminal necrosis [71]. Useful immunohistochemical markers for pancreatic ductal adenocarcinoma include cytokeratin 7 (CK 7), CK 19, mesothelin, placental S100 (S100P), E-cadherin, insulin-like growth factor II messenger RNA-binding protein-3 (IMP3) and mammary serine protease inhibitor (MASPIN) [72]. Loss of DPC4/SMAD4 may be encountered in up to 55% of patients [70].

Recently an integrated genomic expression analysis of 456 pancreatic ductal adenocarcinomas convincingly demonstrated that pancreatic ductal adenocarcinoma represents four distinct subtypes: squamous, pancreatic progenitor, aberrantly differentiated endocrine exocrine (ADEX) and immunogenic types [73].

Periampullary cancers, on the other hand, can broadly be divided into intestinal or pancreatobiliary based on the type of differentiation [74]. The intestinal subtype

Table 16.2 Risk factors for sporadic pancreatic cancer

Risk factor	Estimated risk	Implication	References
Smoking	OR—2.2 (95% CI 1.7–2.8)	75% increased risk compared to non-smokers Reduced risk only after 10 years of cessation Active and early smoking—risk factor for early-onset pancreatic cancer (≤50 years)	[28, 46, 47]
Alcohol	OR—HR 1.62 (95% CI 1.04–2.54)	Positive association between heavy alcohol consumption (≥9 drinks per day) and risk of pancreatic cancer Dose- and age-dependent effect on the development of early (<60 years)- and very early (<45 years)-onset pancreatic cancer	[48–50]
Diabetes mellitus	OR—1.8 (95% CI 1.5–2.1)	1.5–2-fold increase in risk Risk is highest in initial 3 months (HR—3.71) and drops, although still significant (HR—1.65), at 10 years from onset Diabetes is associated with a worse survival	[51–55]
Obesity	OR—1.33 (95% CI 1.12–1.58)	Independent risk factor Centralized fat distribution may increase risk, especially in women	[56, 57]
Chronic pancreatitis	Tropical RR—100 (95% CI 37–218) Hereditary RR—54 (95% CI 35–90)	Accounts for up to 5% of cases Amongst alcoholic CP patients—eightfold increased risk after a mean of 7.4 years Higher risk amongst concurrent smokers	[58–63]
Primary sclerosing cholangitis	Pancreatic cancer OR—11.22 (95% CI 4.11–30.62) Cholangiocarcinoma OR—55.31 (95% CI 22.20–137.80)	398-fold increased risk of developing cholangiocarcinoma	[64, 65]

OR odds ratio, *CI* confidence interval, *RR* relative risk, *TCP* tropical chronic pancreatitis, *CP* chronic pancreatitis, *HR* hazard ratio

is characterized by tubular or cribriform glands and resembles colorectal adenocarcinomas with an attendant relatively better prognosis. The pancreatobiliary subtype, on the other hand, is characterized by glands associated with abundant desmoplastic stroma resembling tumours of the pancreas or extrahepatic bile ducts with an attendant worse prognosis [74–76]. Further delineation of the microscopic subtypes can be achieved by the use of immunohistochemical markers. The 'intestinal subtype' is either (1) stain positive for CK20 or CDX2 or MUC2 and negative for MUC1 or (2) stain positive for CK20, CDX2 and MUC2, irrespective of the MUC1 result, while

the 'pancreatobiliary subtype' is stain positive for MUC1 and negative for CDX2 and MUC2, irrespective of CK20 results [77].

16.3.1 Precursor Lesions

16.3.1.1 Pancreatic Intraepithelial Neoplasia (PanIN)

These premalignant microscopic (usually <5 mm) flat or papillary lesions are lined by columnar or cuboidal with varying amounts of mucin and arise in the smaller intralobular ducts of the head of pancreas more frequently than in the tail region [78–80]. They have been classified into three grades [68, 80, 81] ranging from less invasive to invasive nature. The low-grade PanIN-1A (flat) and 1B (papillary) are lined by columnar epithelial cells and possess minimal cytological or architectural atypia. Intermediate-grade PanIN-2 lesions have loss of nuclear polarity, nuclear crowding, variation in nuclear size (pleomorphism), nuclear hyperchromasia and nuclear pseudostratification with frequent papillae, while the high-grade PanIN-3, also referred to as carcinoma in situ, demonstrate high-grade dysplastic changes in cytology (enlarged, pleomorphic and poorly oriented nuclei with prominent nucleoli and abnormal mitoses) and architecture (characterized by the formation of papillae and cribriform structures sometimes having clusters of cells bud off of the epithelium into the ductal lumen) [68, 82].

These premalignant lesions have been found to possess KRAS and TP53 mutations similar to pancreatic cancer [83]. The immunohistochemical marker MUC1 is almost exclusively expressed in PanINs 2 and 3 [82].

Three characteristics of PanINs include their association with lobulocentric atrophy as well as acinar to ductal metaplasia and the tendency for being multifocal, more commonly in individuals with a strong family history [68, 84, 85].

16.3.1.2 PanINs, Carcinogenesis and Signalling Pathways

Maitra and colleagues [86] suggested that there exists a well-defined pathway in pancreatic carcinogenesis (PanINgram) leading from the precursor lesions (PanINs) to invasive adenocarcinoma as a result of the accumulation of molecular alterations seen with increasing grades of dysplasia. Yachida and colleagues [87] further elucidated the four main driver genes in pancreatic carcinogenesis, namely, KRAS, CDKN2A inactivation, TP53 and SMAD4 inactivation, the latter being associated with an increased risk for tumour dissemination and likely early failure following surgery [88]. Jones and colleagues [89], in addition to confirming that the above 4 genes were mutated at the highest frequency, identified 12 core signalling pathways in pancreatic carcinogenesis based on a global genomic analysis. These included KRAS, TGF β, Wnt/Notch, hedgehog, integrin, JNK and small GTPase signalling pathways in addition to the pathways involved in apoptosis, DNA damage control, invasion, homophilic cell adhesion and control of G1/S phase transition.

16.3.2 Pathological Assessment of the Resected Pancreatic Cancer Specimen

While not precisely defined in surgical practice, tumours of the pancreas have been anatomically subdivided, based on location, into tumours of the head of pancreas (arising to the right of the left border of the superior mesenteric vein and including the uncinate process), tumours of the body of pancreas (arising between the left border of the superior mesenteric vein and the left border of the aorta) and tumours of the tail of pancreas (arising between the left border of the aorta and the splenic hilum) [90].

A margin-negative (R0) resection is regarded as the surgeon's best contribution to pancreatic cancer patients [91]. In 2008, Esposito and colleagues [92] demonstrated that the adoption of a standardized pathology reporting of resected specimens was able to pick up previously underappreciated margin positivity. This led to a concerted effort towards the reporting of pathological specimens. Central to pathological reporting is the recognition that resected pancreatic cancer, more specifically the pancreatoduodenectomy (PD) specimen, has four relevant margins [93, 94]:

(a) The luminal margins (proximal gastric or duodenal and distal jejunal)
(b) Bile duct margin (BDM)—common bile duct or common hepatic duct margin
(c) Pancreatic transection margin (PTM)
(d) Pancreatic circumferential or radial margin (CRM)—which further includes:
    1. Pancreatic anterior margin (PAM)—anterior surface
    2. Pancreatic posterior margin (PPM)—posterior surface
    3. Pancreatic medial margin (PMM)—surface facing the superior mesenteric vessels

There exists variability in the terminology used for the CRM with European pathologists favouring the terms PPM and PMM, while the American pathologists use the terms 'deep retroperitoneal posterior surface' and 'uncinate process' margins [93]. Some of the standardized protocols currently followed are the Leeds Pathology Protocol (LEEPP) [95] and the protocols provided by the College of American Pathologists (CAP) [96], the Royal College of Pathologists [97] and the American Joint Committee on Cancer (AJCC) [90].

In general, the entire pancreatic head specimens are serially sliced in a plane perpendicular to the longitudinal axis of the duodenum thereby avoiding opening the biliary or pancreatic duct [95]. The advantage of this technique is that it permits an extensive study of the lesion and its relationship with anatomical structures and surgical margins [93]. All the above-named margins must preferentially be inked.

The final controversy in pathological specimen reporting relates to what is considered a microscopically positive margin (R1). Majority of American pathologists

regard a margin to be positive only when the tumour is directly in contact with the inked margin (0 mm clearance) [98], while European pathologists, borrowing on experience from rectal cancer assessment, label a tumour as R1 when the distance between the tumour and the resection margin is ≤1 mm [97]. The Royal College of Pathologists puts this into perspective by appreciating that for the PAM, a 0 mm clearance would be regarded as adequate clearance since it is an anatomical surface rather than a true margin, while for the other margins, the tumour is deemed incompletely excised if the margin is ≤1 mm [97].

16.4 Staging

Table 16.3 provides the seventh edition of the TNM Classification of Pancreatic Cancer as per the American Joint Committee on Cancer staging [90], while Table 16.4 details the changes proposed in the eight edition of the TNM Classification [99].

Table 16.3 Seventh edition of the American Joint Committee on Cancer staging of exocrine pancreatic cancer [90]

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No e/o primary tumour		
Tis	Carcinoma in situ		
T1	Tumour limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumour limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph nodal metastasis		
N1	Regional lymph node metastasis		
Distant metastases (M)			
M0	No distant metastases		
M1	Distant metastases		
Anatomic stage			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Table 16.4 Proposed eighth edition of the American Joint Committee on Cancer staging of exocrine pancreatic cancer [99]

Primary tumour (T)			
TX	Primary tumour cannot be assessed		
T0	No e/o primary tumour		
Tis	Carcinoma in situ		
T1	Maximum tumour diameter <2 cm		
T2	Maximum tumour diameter > 2 ≤ 4 cm		
T3	Maximum tumour diameter >4 cm		
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph nodal metastasis		
N1	Metastasis in 1–3 regional lymph nodes		
N2	Metastasis in ≥4 regional lymph nodes		
Distant metastases (M)			
M0	No distant metastases		
M1	Distant metastases		
Anatomic stage			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	Any T	N2	M1
	T4	Any N	M0
Stage IV	Any T	Any N	M1

16.4.1 Signs and Symptoms of Pancreatic Cancer [100, 101]

The early symptoms of pancreatic head cancer are rather non-specific leading to patients presenting late with painless progressive jaundice, back pain (from retroperitoneal invasion), weight loss and asthenia and anorexia and vomiting (owing to gastroduodenal invasion). In the author's own experience of patients amenable to Whipple's resection, the most common presenting symptoms were obstructive jaundice (60%) and abdominal pain (50%).

Tumours of the body and tail are even more notorious for a delayed presentation. The reason for this is that the bile duct is away and thus by the time the patient develops symptoms of gastric outlet obstruction or back pain or a palpable lump, the tumour has already disseminated [102]. Important symptoms to be aware of in these patients are new onset diabetes mellitus, especially after the age of 60 years, and epigastric pain radiating to the back akin to an episode of acute pancreatitis [102].

Cancers of the lower bile duct and ampulla of Vater generally present early as painless jaundice (>80%; author's own data of patients with resectable tumours) with or without cholangitis as these lesions obstruct the biliary passages early in the

course of the disease. The sine qua non of 'waxing and waning' of obstructive jaundice is encountered in only one-third patients [103]. Patients with duodenal tumours (included under the definition of periampullary tumours) may present with abdominal pain and/or vomiting.

As noted above, chronic pancreatitis is a risk factor for cancer. Thus in patients with chronic pancreatitis for more than 10 years, the development of 'new symptoms' such as sudden and severe weight loss in a controlled diabetic or the development of jaundice or change in the nature of pain should alert the clinician to evaluate the patient for an underlying neoplastic process [63].

Fever may sometimes be the first symptom that brings the patient to the clinician owing to underlying cholangitis especially in periampullary tumours.

Important clinical signs in patients with cancers of the pancreas and periampullary region include icterus and other signs of obstructive jaundice such as high-coloured urine and pale stools in the absence of choledocholithiasis and scratch marks on the trunk and extremities owing to the pruritus from the cuticular deposition of bile salts. A palpable gallbladder is a sign of an underlying pancreatic head cancer (Courvoisier's law), while a palpable lump in the epigastrium or left hypochondrium may be the first sign of a tumour of the body and tail.

Clinical features in keeping with advanced cancer are the enlarged supraclavicular (Virchow) lymph node, Blumer's shelf on digital rectal examination and ascites.

16.4.2 Investigations

An abdominal ultrasound is generally the first investigation advised when a patient presents with complaints of an abdominal lump or signs and symptoms of jaundice. Findings suspicious of a pancreatic or periampullary malignancy include a dilated common bile duct (>6 mm pre-cholecystectomy or >10 mm post-cholecystectomy [104, 105]) devoid of gallstones, mass in the pancreas with or without liver metastases or ascites. In patients with a poor functional status with pancreatic mass and liver metastases and/or ascites, a fine needle aspiration or ascitic fluid cytology to confirm malignancy may be all that is required taking into consideration the wishes of the patient. However, in patients with findings suspicious of a pancreatic cancer and a good functional status, a complete work-up would include the following.

16.4.2.1 Serology

These investigations are not diagnostic of pancreatic cancer but are of value when planning therapy.

(a) Complete blood counts—anaemia, as a result of occult bleeding, may be encountered in patients with periampullary tumours as these tumours are probe to slough off. In patients with cholangitis, the white cell count is elevated and supports the decision for biliary drainage as the first intervention.

(b) Liver function tests—elevations in serum bilirubin and liver enzymes are encountered in patients with surgical obstructive jaundice. A low serum albumin level in the preoperative setting has been found to correlate with a worse disease-free and overall survival in patients with pancreatic cancer [106].
(c) Renal function tests—patients with chronic renal impairment are at increased risk of perioperative complications especially if their creatinine levels are >2 mg/dL [107].
(d) Prothrombin time and international normalized ratio (INR)—patients with surgical obstructive jaundice must be assessed for coagulopathy as this not only is important from a surgical perspective but also for the preoperative placement of the epidural catheter [108].
(e) Blood sugar levels—new onset diabetes mellitus (within the preceding 2 years) may be encountered in up to 68% of patients with pancreatic cancer [108].

16.4.2.2 Tumour Markers

(a) Serum carbohydrate antigen 19-9 (CA 19-9)

Serum CA 19-9 has a median sensitivity of 79 (70–90%) and a median specificity of 82 (68–91%) for the diagnosis of pancreatic cancer [109]. Although elevated levels of CA 19-9 are generally associated with decreased stage-specific survival (>37 U/mL) [110] and locoregional failure-free survival (>200 U/mL) [111], this is of most significance in anatomically resectable, early-stage pancreatic cancer [110]. This finding has prompted some clinicians to suggest the role for neoadjuvant therapy in this specific subgroup of patients [110]. In patients with borderline resectable or locally advanced disease, normalization of CA 19-9 levels after commencing neoadjuvant therapy may help in guiding the further course of therapy, early surgery over further therapy [112, 113]. Normalization of CA 19-9 levels post surgical resection is predictive of better disease-free survival [114] and may help in the further surveillance for disease recurrence in this patient subset.

Thus, routine analysis of serum CA 19-9 levels is advisable at diagnosis of the cancer since there is some data to support its role as a diagnostic biomarker, although its utility is more as a marker to predict tumour stage, resectability, overall survival and response to therapy [115].

Caution is advised when interpreting elevated CA 19-9 levels in patients with cholestasis [116] where false-positive elevations have been noted and those patients who are Lewis blood group antigen negative and thus unable to secrete CA 19-9 [117].

Various other markers have been tested in pancreatic cancer including carcinoembryonic antigen (CEA), CA 242, CA 125 and CA 72-4. However, they are of limited utility owing to their sensitivities being lower than CA 19-9 [118].

16.4.2.3 Radiological Investigations

(a) Pancreas protocol multi-detector computed tomography (MDCT) scan of the abdomen and pelvis with multiplanar reconstruction (Figs. 16.1, 16.2 and 16.3)—This is currently the best available modality for assessing the primary tumour, its locoregional and distant intra-abdominal spread as well as the vascular anatomy

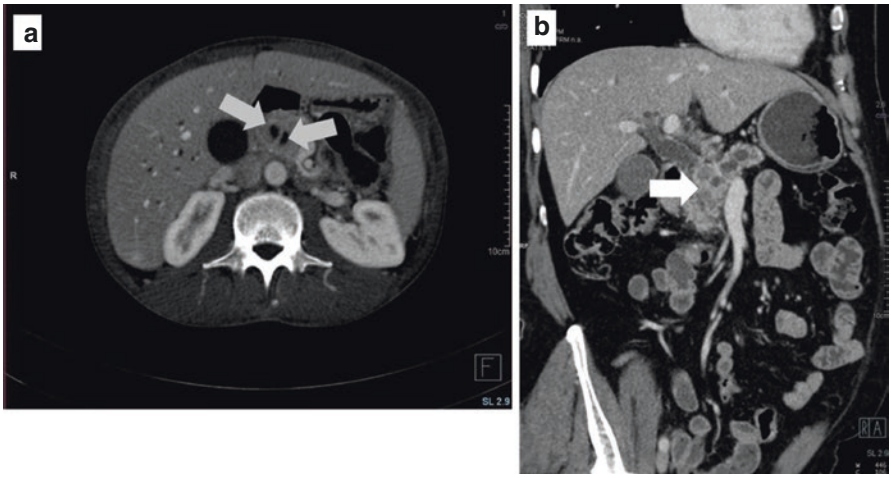

Fig. 16.1 Multi-detector computed tomography images demonstrating the 'double duct' sign—upstream dilation of the common bile duct (CBD) and main pancreatic duct (MPD) as a result of an obstructing periampullary tumour—(**a**) axial post-contrast section (CBD and MPD marked with bold grey arrows) and (**b**) coronal reformation (tumour marked with white arrow)

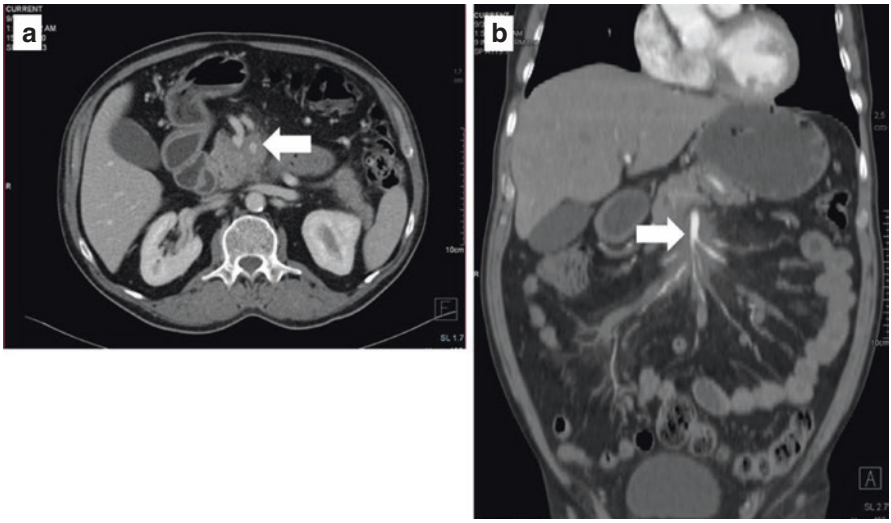

Fig. 16.2 Multi-detector computed tomography images demonstrating a locally advanced pancreatic uncinate process cancer that has infiltrated the root of mesentery resulting in a complete encasement of the superior mesenteric artery (SMA) and its jejunal branches—(**a**) axial post-contrast section (encased SMA marked with white arrow) and (**b**) coronal reformation (encased SMA marked with white arrow)

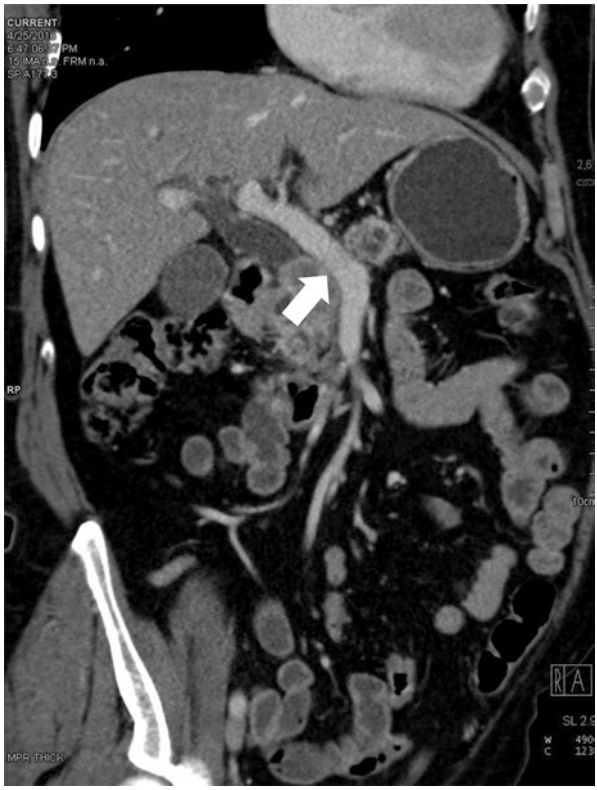

Fig. 16.3 Coronal reformation on a multi-detector computed tomography scanner image demonstrating a mass lesion in the head of pancreas abutting the distal superior mesenteric vein (SMV) marked with white arrow—borderline resectable pancreatic cancer

(an essential component of pre-surgical planning [119]). The pancreas protocol CT scan comprises a pre-contrast scan and three post-contrast phases with axial section thickness ≤5 mm [120] and water or mannitol as the negative contrast to distend the stomach and duodenum and permit delineation from the pancreas:

1. Pre-contrast scan—enables the detection evaluation of pancreatic calcifications and permits determination of the precise levels for imaging on the post-contrast phases.
2. Arterial phase—the first of the post-contrast phases obtained at 20–30 s (depending on the injection rate 5–3 mL/s [121]) permits an accurate evaluation of the pancreatic vascular anatomy without interference from venous opacification [120].
3. Pancreatic parenchymal phase—previously termed late arterial phase, is obtained at 40–50 s (depending on the injection rate 5–3 mL/s [121]). Owing to marked difference in enhancement between the maximally enhanced pancreatic parenchyma and the generally hypoenhancing pancreatic cancer, this phase allows an assessment of the tumour and its relation to the surrounding structures including vessels.
4. Portal venous phase—also termed hepatic phase, these images are obtained at 60–70 s (depending on the injection rate 5–3 mL/s [121]). This phase helps in assessing venous involvement and also hypovascular liver metastases.

(b) Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP)—may be an alternative to MDCT in case facilities for performing, or the expertise needed to report a CT scan, are not available.

MDCT scans are better suited as compared to MRI for the detection of pancreatic cancers as well as the assessment of nodal and distant spread and vascular involvement [122]. The only small subset of patients in whom an MRI may outperform CT scans is in the assessment of isoattenuating cancers [123]. However, it must be clearly stated that the accuracy of either investigation still falls well short of perfection especially in terms of detecting lesions <2 cm [122] as well as in the accurate characterization of venous involvement [124] and diagnosis of peritoneal and small surface liver metastases. Whether dual-energy CT scans [125] will overcome some of these shortcomings remains to be confirmed. Until then, the reliance on complementary investigative modalities such as endoscopic ultrasound (EUS), positron emission tomography-CT (PET-CT), venography and even staging laparoscopy is imperative.

(c) Chest X-ray—to rule out lung metastases.

16.4.2.4 Endoscopy

(a) Side-viewing endoscopy (Fig. 16.4)—is useful to obtain biopsies of ampullary and duodenal carcinomas. Novel technologies such as narrow band imaging (NBI) help to differentiate between ampullary adenomas and adenocarcinomas with an accuracy approaching 80% [126, 127]. Such information is vital when deciding on local endoscopic excisions versus directly offering surgery to these patients.

(b) Endoscopic retrograde cholangiopancreatography/ERCP—to obtain biliary cytology for diagnosis. Given the declining diagnostic role for ERCP, the main indication is the relief of biliary obstruction and placement of stents (Fig. 16.5) in patients with cholangitis. Such a strategy is valuable preoperatively in patients with cholangitis with or without renal impairment or in those unfit for surgery in

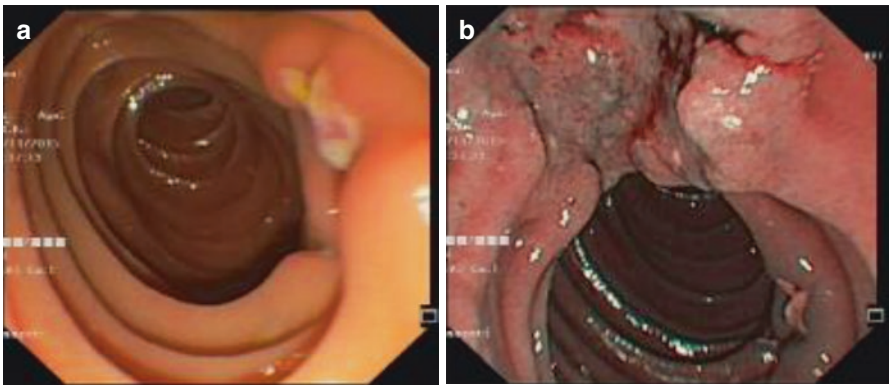

Fig. 16.4 Ampullary mass images on endoscopy—(**a**) side-viewing image showing an ulcerated mass at the ampulla of Vater and (**b**) the same lesion on narrow band imaging

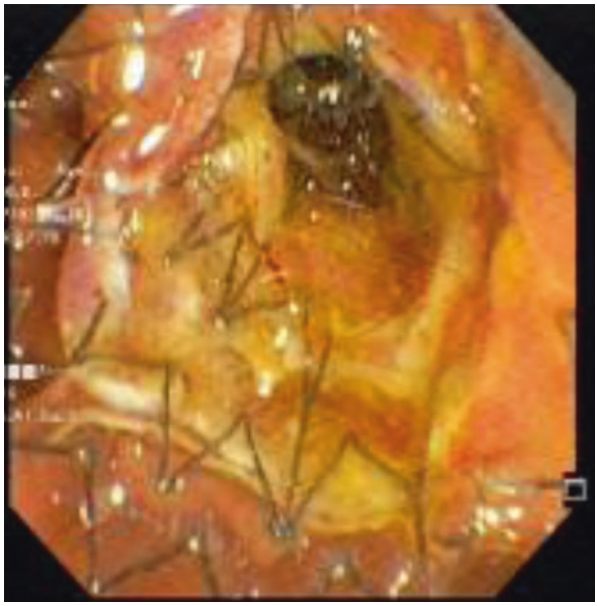

Fig. 16.5 Side-viewing endoscopic image of a successfully deployed SEMS placed across a malignant lower CBD stricture

whom optimization prior to surgery is essential or as a definitive procedure for biliary obstruction in patients with an unresectable lesion [128–130]. Endobiliary drainage results in biliary colonization with rates reported to be around 64% [131]. Thus, it should be preferably performed only in the above situations and not in every patient who presents with surgical obstructive jaundice since it is associated with an increased risk of surgical site infections [132], increased hospital stay and increased costs [133]. While there is no standard time frame for performing surgery following endobiliary drainage, the period of 4–6 weeks to permit the attendant inflammation to settle is generally accepted [128].

In terms of the choice of stent, short-length self-expandable metal biliary stents (SEMS) are preferred to plastic stents if extended delays (>6 weeks) are anticipated between the stenting and PD [134, 135]. In terms of long-term palliation of biliary obstruction, too, SEMS are preferred [136] as the durability of the stent offsets the initially perceived increased costs [137].

(c) Endoscopic ultrasonography/EUS (Figs. 16.6 and 16.7)—EUS has steadily emerged as one of the most useful complementary tools to standard imaging. It is not only of value in delineating lesions <2 cm [138]; EUS is the best available modality for the accurate T-staging of pancreatic cancer with sensitivities approaching 72% for T1-2 lesions and 90% for T3-4 lesions [139]. It is useful in obtaining cytology (EUS—fine needle aspiration) for histopathological as well as molecular analysis to aid in confirming the diagnosis of malignancy which is of prime importance to patients who have unresectable/borderline resectable or metastatic disease and also to assess suspected vascular involvement in CT or MRI. EUS has a superior sensitivity as compared to CT scan (69% versus 48%) for the detection of vascular involvement by the tumour [140].

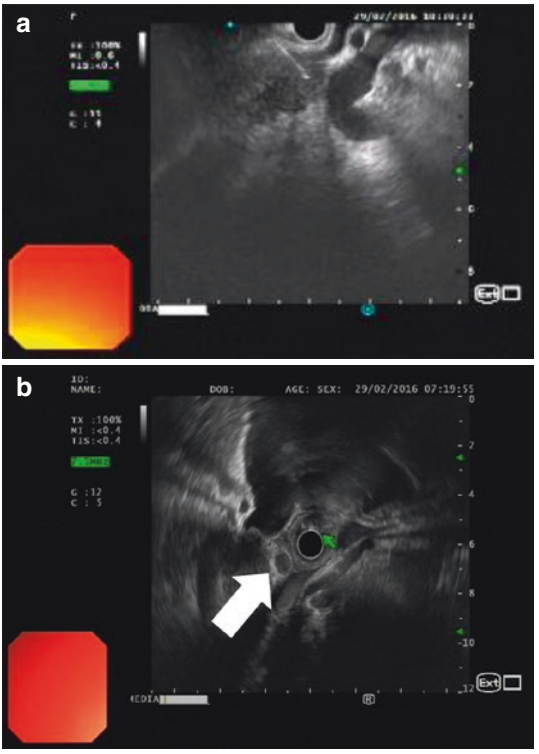

Fig. 16.6 (**a**) Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) with a 22-gauge needle of a pancreatic head mass. (**b**) A peripancreatic lymph node (marked with a white arrow) oval in shape with irregular borders depicted on EUS—such lymph nodes can also be subjected to FNA

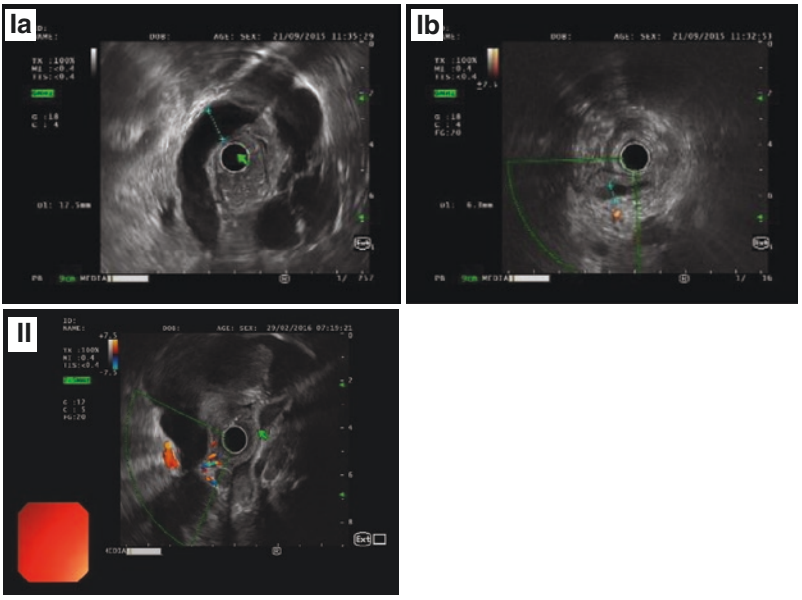

Fig. 16.7 Endoscopic ultrasound (EUS) images obtained with a radial endoscope using 7.5 MHz frequency depicting (I) a resectable ampullary tumour causing upstream dilation of (**a**) the CBD and (**b**) the MPD. (II) Portal vein invasion

16.4.2.5 Complementary Investigations

(a) Positron emission tomography in combination with CT (PET-CT) or MRI (PET-MRI)—was initially regarded as a useful adjunct to MDCT or MRI in patients with locally advanced or borderline resectable tumours to detect or rule out metastases outside the abdominal cavity [141]. However, there is steadily emerging evidence that PET imaging parameters such as standardized uptake values (SUV max) on CT [142] or the minimal apparent diffusion coefficient (ADC_{min}) [143] correlate with survival in patients with resectable and metastatic disease [144]. PET-CT is also useful in conjunction with MDCT to detect tumour recurrences on follow-up [145]. PET-CT is now recommended for routine staging of resectable pancreatic cancer.

(b) Staging laparoscopy (SL) and laparoscopic ultrasonography—the best indication for staging laparoscopy in pancreatic cancer is in the assessment of patients with non-metastatic, unresectable or borderline resectable disease on conventional imaging. In this subset of patients, SL will help detect occult liver and/or peritoneal metastases (sensitivities of 88% and 93%, respectively) [146] or confirm their non-metastatic nature and hence help direct patients towards neoadjuvant treatment protocols [147]. When used in all patients with pancreatic cancer, SL with ultrasound correctly predicted resectability in 79% compared to 55% by standard imaging, thereby avoiding non-curative laparotomies in 33% of patients [148].

(c) Venography [149]—this modality consists of images obtained either by CT scan, superior mesenteric arteriography or intraoperative portal venography following cannulation of a superior mesenteric venous tributary. Venous involvement has been classified as type A (no narrowing), B (unilateral narrowing), C (bilateral narrowing) and D (stenosis or obstruction with collaterals). The correlation with histology was noted in 100% of patients with type A (no invasion), while invasion was present in 51%, 74% and 93% of patients with types B, C and D, respectively.

16.4.3 Surgical Management

Surgery offers the only chance of cure in patients with pancreatic and periampullary cancer. However, it should only be attempted in patients in whom a complete (R0) resection is deemed feasible. The available evidence does not support the role for gross margin-positive (R2) resections. Endoscopic ampullary excisions may be considered only in benign lesions. For lesions harbouring a malignancy, a pancreatoduodenectomy (PD) must be performed as nearly 30% of patients with T1 lesions harbour lymph node metastasis [150].

From a surgical perspective, pancreatic cancers can be classified as resectable, borderline resectable, locally advanced and metastatic depending on the tumour extent and contact with or involvement of adjacent blood vessels (superior mesenteric artery or vein/SMV or SMA, hepatic artery/HA, celiac axis, portal vein/PV). The term ‘resectable’ pancreatic cancer has been loosely used to include all tumours amenable to a resection irrespective of whether this resection would entail a synchronous vascular resection. The advent of the anatomical term *borderline resectable* pancreatic tumour or cancer (BRT) to include tumours with limited involvement

of the mesenteric vessels (abut SMA, abut or encase common HA over a short segment or occlude SMV-PV confluence), in which a resection with venous reconstruction is technically possible but which carry a high risk of margin-positive resection unless neoadjuvant therapy is employed before surgery [151, 152], has certainly been useful. It has enabled a clearer delineation of locally advanced but non-metastatic (unresectable) cancers from those tumours in whom a resection can be contemplated with hope of providing a survival benefit.

The surgery for pancreatic head and neck cancers is a PD, while a distal or subtotal pancreatectomy (with splenectomy) is performed for cancers of the distal neck, body and tail.

Perioperative antibiotic prophylaxis must be considered in all patients undergoing pancreatoduodenectomy owing to the risk of bactibilia (12–18%) [131, 153] even in those who have not undergone prior biliary intervention.

16.4.3.1 Pancreatoduodenectomy (PD)

The Resection

PD (Fig. 16.8) involves removal of the stomach and duodenum, the pancreatic head, uncinate process and neck along with the distal common bile duct (and gallbladder)

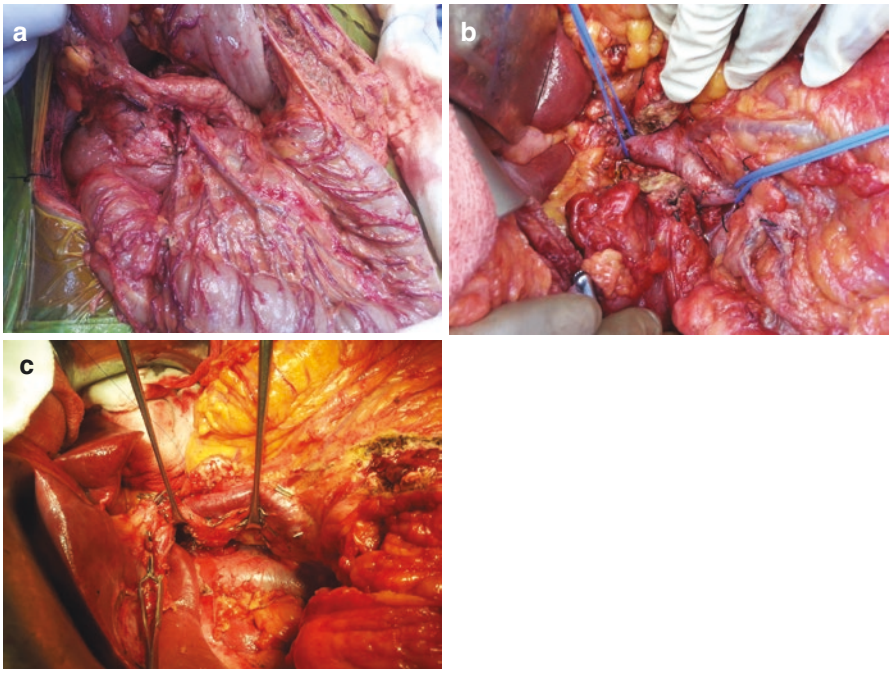

Fig. 16.8 Intraoperative photographs depicting (**a**) completed dissection of the pancreatic neck tunnel, (**b**) transected pancreatic neck with the portal vein (cranial) and SMV (caudal) with blue vessel loops and (**c**) completed Whipple's resection with the SMA being retracted by a vein loop

and the first few inches of the jejunum. Based on the location of the proximal margin of transection (stomach or pyloro-duodenum), there are two named procedures, viz. the classical Whipple's procedure (proximal transection at the junction of distal body and antrum of the stomach) and the pylorus-preserving PD (PPPD). Distally, up to 15 cm of the jejunum (from the duodeno-jejunal flexure) may be resected. It is important for every surgeon to identify the portal vascular anatomy to avoid inadvertent injury to aberrant vessels [119]. It is preferred that the mesopancreatic tissue in the region of the uncinate process be divided between ligatures/LIGACLIPS®. In a broad uncinate process, surgeons have successfully employed the use of endovascular staplers after ensuring adequate clearance from the cancer without compromising the radicality of the procedure [154]. In such a scenario, the author would advise that the operating surgeon thoroughly inspect the staple line prior to commencing the pancreaticoenteric anastomosis as there is a tendency for small vessels to bleed. These can be secured with 4-0 polypropylene sutures. Alternatively, the Ligasure® or harmonic scalpel may be used to divide the mesopancreatic tissue.

The Reconstruction

At the end of the resection, the surgeon is faced with a transected pancreas, transected bile or hepatic duct and remnant stomach. The reconstruction following PD progresses in an anti-clockwise manner commencing with the pancreaticoenteric anastomosis followed by the hepatico-enteric and finally the gastro-enterostomy. While the common hepatic duct and stomach are anastomosed to the jejunum (hepaticojejunostomy/HJ and gastrojejunostomy/GJ), the choice of anastomosis of the pancreatic remnant is between the stomach (pancreaticogastrostomy/PG) and the loop of jejunum (pancreaticojejunostomy/PJ). The PG/PJ and HJ are always behind (retrocolic) the transverse colon, while the GJ may be performed antecolic (in front of) or retrocolic.

The existing literature, including the most updated Cochrane review, indicates that there is no difference in terms of oncological benefit, overall morbidity and mortality when PPPD was compared to a classical Whipple's procedure [155]. However, on closer inspection of the data, while the review indicated that delayed gastric emptying (DGE) was higher in PPPD, pylorus preservation was associated with shorter operating times, lower intraoperative blood loss and hence a reduced need for blood transfusion [155]. The studies included in this analysis were heterogenous with no uniform information provided regarding intention-to-treat, use of adjuvant and neoadjuvant therapy, etc. Thus, this remains an area that warrants future well-designed trials [156]. Despite this, it must be borne in mind that in specific situations such as duodenal cancers or large pancreatic head tumours invading the gastric antrum and/or the first part of the duodenum, a classical PD should be performed.

The most recent meta-analysis has concluded that there exists no difference in the rate of overall and clinically significant post-operative pancreatic fistula (POPF), morbidity, mortality, reoperation and intra-abdominal sepsis between PG and PJ [157]. Similarly, while the duct-to-mucosa PJ has been shown to reduce duration of hospital stay, it did not significantly reduce rates of pancreatic fistula and other adverse events as compared to invagination PJ [158]. Thus, the focus of a

pancreaticoenteric anastomosis must be on the performance of a standardized, meticulous anastomosis [159] based on sound surgical principles.

Performance of an antecolic gastro- or duodeno-jejunostomy after PD is associated with a reduction in the rate of DGE as well as post-operative days to start a diet and length of hospital stay as compared to a retrocolic reconstruction [160].

Lymphadenectomy is central to the oncological completeness (staging and survival) of PD for pancreatic cancer as in the case of other solid organ cancers. A standard lymphadenectomy involves removal of stations 5, 6 and 8a along with lymph nodes of the right side of the hepatoduodenal ligament (12b1, 12b2, 12c), posterior pancreaticoduodenal nodes (13a, 13b), nodes to the right side of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreaticoduodenal artery (14a, 14b) and anterior pancreaticoduodenal nodes (17a, 17b) [161]. The existing literature suggests that a standard lymphadenectomy is not only associated with a lower morbidity (increased risk of intractable diarrhoea in the early post-operative phase seen with extended lymphadenectomy) but also comparable survival compared to an extended lymphadenectomy [162].

16.4.3.2 Distal/Subtotal Pancreatectomy

While surgeries such as spleen-preserving distal pancreatectomy as well as middle or central pancreatectomy may be considered in benign or borderline malignant lesions of the neck, body and tail of the pancreas, depending on the location of the tumour, the standard procedure for a pancreatic cancer involving the distal neck, body and/or tail is a distal/subtotal pancreatectomy with splenectomy [163, 164].

Cancers of the body and tail of pancreas are notorious for presenting at an advanced stage. If not yet metastatic at presentation, in up to one-third of patients, the tumours at surgery have evidence of involvement of surrounding organs either as a result of direct tumour infiltration or inflammatory adhesions [165]. In such patients, an en bloc resection (including multivisceral resections) in these patients should be attempted so long as a complete (R0) resection can be achieved. There is evidence to suggest that in patients undergoing an R0 resection, the long-term survival rates are similar to patients undergoing standard resection for resectable tumours [166–168] and markedly improved as compared to patients with unresectable locally advanced disease [167]. Given the high morbidity and risk of mortality associated with these resections, they should preferably be undertaken in high-volume centres [169].

Owing to the high frequency of POPF following distal pancreatic resections, there has been a focus on whether the method of transection (staplers or suture, use of ultrasonic dissection devices) or the re-enforcement of the pancreatic stump with mesh or glue improves outcomes. The results of Cochrane systematic review, largely influenced by a single multicentre randomized controlled trial (DISPACT) [170], concluded that the outcomes following hand-sewn closure of the pancreatic remnant after stapled or scalpel resection are comparable in terms of POPF, overall mortality and surgical time [171]. While the available evidence does support practices such as the use of ultrasonic dissection devices or re-enforcement of the pancreatic remnant with glue or mesh [172], it must be appreciated that the data is sparse and fraught with heterogeneity that precludes the generation of firm conclusions. Irrespective of

the technique used to transect/close the pancreatic stump, meticulous attention needs to be paid to transfixing the pancreatic duct.

Removal of lymph node stations 10, 11 and 18 is considered part of a standard lymphadenectomy for lesions in the pancreatic body and tail [161].

16.4.3.3 Borderline Resectable Tumours (BRT)

Maurer and colleagues [173] were the first to appreciate that some cancers of the pancreas may not be completely resectable at the outset but may be so after neoadjuvant therapy. This entity was christened BRT by the group from the MD Anderson Cancer Center [151]. The definition of BRT has evolved over the years (Table 16.5) [151, 174–177]. The outstanding issues with managing BRT are whether to offer upfront surgery or neoadjuvant therapy; if neoadjuvant therapy is to be used, then should it include chemotherapy only or chemotherapy with radiotherapy; what is the ideal regimen of chemotherapy to be used; and finally what is the true benefit of embarking on such resections in terms of survival improvement. The rationale behind recommending neoadjuvant therapy in BRT was to increase the rate of R0 resections [152]. However, the neoadjuvant chemotherapy protocols such as FOLFIRINOX (5-fluorouracil + oxaliplatin + irinotecan + leucovorin) are quite toxic, and the preliminary results from the ongoing ALLIANCE trial [178] suggest that the improvement in resection rates may not be significantly increased. The issues regarding vascular resections are discussed below. Besides, restaging of BRT post-neoadjuvant therapy is fraught with difficulties in interpretation owing to desmoplastic/inflammatory changes in and around the tumour and pancreas which could either be from the tumour or therapy induced [179]. Thus, the consensus regarding the optimum management strategy for BRT remains ‘a work in progress’. However, if a patient presents with features clearly indicative of BRT as per radiological features, then such patients must be considered for a staging laparoscopy followed by neoadjuvant chemotherapy (if non-metastatic) followed by a trial of resection (if the disease remains non-progressive) with the need for synchronous venous resection and reconstruction. The role of studying genetic markers such as SMAD4 (to help in decision-making) needs to be addressed in this subset of patients [88, 180].

Vascular Resections

Arterial and venous resections have been performed as part of pancreatic resections for a few decades [181] with the rationale that they are beneficial so long as an R0 resection could be achieved [182]. In the case of distal pancreatic resections, there have been reports of 28 highly selected patients undergoing synchronous celiac artery resections with (bypass from the aorta to the common hepatic artery) or without relying on the presence of collateral arterial circulation via an intact pancreaticoduodenal arcade and the gastroduodenal artery to maintain prograde hepatic arterial perfusion reconstruction (modified Appleby procedure) [183].

However, recent analyses made surgeons rethink the true benefit of such resections. Synchronous arterial resections are associated with higher R2 margin rates [184], an increased risk of perioperative morbidity and mortality [185] and survival rates comparable to non-resected patients with locally advanced and non-metastatic disease [184, 186]. The most recent meta-analysis has demonstrated the same results with synchronous venous resections [187]. The reasons for the findings of

Table 16.5 Variations in the definition of borderline resectable pancreatic cancer (Reproduced with permission from Barreto SG, Windsor J. Justifying vein resection with Pancreatoduodenectomy. Lancet Oncol 2016; 17: e118–24)

Organization(s)	MD Anderson Cancer Center	Americas Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology	National Comprehensive Cancer Network	Intergroup trial (Alliance A021101)	American Pancreatic Association[a]
Year	2006	2009	2012	2013	2014
Author (ref)	Varadhachary et al. [151]	Callery et al. [174]	Tempero et al. [175]	Katz et al. [176]	Al-Hawary et al. [177]
SMV-PV	Short-segment occlusion of SMV, PV or SM-PV confluence with suitable option for vascular reconstruction available because of a normal SMV below and normal PV above area of tumour involvement	Tumour abutment with or without impingement and narrowing of lumen or encasement of SMV-PV or short-segment venous occlusion resulting from either tumour thrombus or encasement but with suitable vessel proximal and distal to vessel involvement, allowing for safe resection and reconstruction	Abutment with impingement or narrowing	Interface between primary tumour and ≥180° of the circumference of SMV-PV and/or short-segment occlusion of SMV-PV with normal vein above and below the level of obstruction amenable to resection and venous reconstruction	Tumour contact of >180° with SMV or PV Tumour contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to site of involvement allowing for safe and complete resection and reconstruction
SMA	Tumour abutment involving ≤180° of circumference	Tumour abutment not to exceed >180°of circumference	Abutment	Interface between tumour and <180° of the circumference of wall	Tumour contact of ≤180°
GDA	–	Encasement	–	–	–

CHA/HA	Short-segment encasement amenable to resection and reconstruction	Either short-segment encasement or direct abutment	Abutment or short-segment encasement	Short-segment interface (of any degree) between tumour and HA with normal artery proximal and distal to the interface amenable to resection and arterial reconstruction	Contact with CHA or HA bifurcation allowing for safe and complete resection and reconstruction
Celiac trunk/axis	No extension	No extension	No abutment or encasement	Interface between tumour and <180° of the circumference	No extension
IVC	–	–	–	–	Tumour contact
Vascular anomalies	–	–	–	–	Tumour contact with variant arterial anatomy (e.g. accessory or replaced RHA or replaced CHA)

[a]Adopted by National Comprehensive Cancer Network in 2015 [40]

SMV superior mesenteric vein, *SMA* superior mesenteric artery, *PV* portal vein, *RHA* right hepatic artery, *IVC* inferior vena cava, *CHA/HA* common hepatic artery/hepatic artery, *GDA* gastroduodenal artery

this meta-analysis as compared to previous studies suggesting a role for venous resections [188] are likely due to the fact that venous resections do not alter outcomes so long as the vein is truly involved, especially the tunica media and intima [189], and if the length of involvement is more than 3 cm [182].

The role of synchronous vascular resections thus needs to be more carefully studied, and such resections performed in highly selected individuals preferably within the confines of clinical trials [185] should be limited to high-volume centres with experienced surgical and multidisciplinary teams [188].

A useful technique in determining whether the vessels are involved early in the course of the surgery is the superior mesenteric 'artery first' approach [190].

16.4.4 Surgery for Metastatic (M1) Disease

There is evidence in literature that pancreatic resections along with, or followed by, removal of oligometastatic disease (interaortocaval lymph nodes, liver and peritoneal metastasis) are feasible [191, 192]. However, the number of patients in the individual reported series is small. Thus, the true impact of such resections in terms of prolonging overall survival remains unclear [193]. More recently, Paiella and colleagues analysed the data on para-aortic lymph node metastases and found that involvement of this group of lymph nodes is associated with a poor prognosis and significantly reduced survival [194]. De Jong and colleagues when analysing their data of 40 patients who underwent resections and/or radiofrequency ablation of periampullary liver metastases inferred that there may be a modest benefit in the intestinal subtype but none in the pancreatobiliary subtype [195].

Thus, such resections must not be performed unless further evidence from well-conducted trials emerges to support such practices.

16.4.5 Laparoscopy and Robotic Surgery for Pancreatic and Periampullary Carcinoma

Minimally invasive surgery (laparoscopy and robotic surgery) has been demonstrated to be feasible in pancreatic surgery. Based on a national observational study, Sulpice and colleagues of the French Pancreatectomy Study Group [196] deduced that distal pancreatectomy has acceptable short- and long-term outcomes although it has not been widely accepted. This has been better elucidated in a well-conducted study of accelerated recovery after laparoscopic distal pancreatectomy that indicated a high readmission rate [197]. Even for PD, the combined experience of the world is barely a thousand cases, and these are performed only in well-selected cases [198]. To date, there exists no level 1 evidence to suggest that minimally invasive pancreatic surgery is equal to, or superior to, open surgery in terms of overall survival for pancreatic and periampullary cancer [199]. Possible reasons for the slow adoption of minimally invasive surgery into pancreatic surgery could be the costs associated, the time taken for individual procedures and the realization that the morbidity associated with pancreatic surgery (POPF, DGE, post-pancreatectomy

haemorrhage/PPH) is unrelated to the length of the abdominal incision but rather to the anastomoses [200].

16.4.5.1 Complications of Pancreatic Surgery

The three most important complications specific to pancreatic surgery are POPF [201], DGE [202] and PPH [203]. Complications following pancreatic surgery are a significant contributor not only to costs but also overall survival [204]. Many of the factors contributing to the occurrence of complications such as a soft pancreas, small duct diameter and comorbidities are beyond the control of the surgeon. Thus, central to reducing complications from a surgeon's perspective is the improvement in the quality of surgery and perioperative care [204]. This would include standardization of technique [159], attention to detail and focus on training [205], regionalization of pancreatic surgeries [206, 207] and implementation of clinical pathways [208, 209]. The role of intraoperatively placed drains in the development of complications has been addressed [210]. While drains certainly do not prevent complications, they aid in the early detection of complications, especially POPF and PPH [211].

16.4.6 Irreversible Electroporation (IRE)

The technique of IRE involves the delivery of high voltage (maximum 3000 V) at small microsecond pulse lengths (70–90 μs) to the tissue. This results in permanent cell death through cell membrane perforation and a further protracted cell death by apoptosis as a result of cellular electrolyte instability [212]. This technique is still in the phase of evolution, and while it has been found to be safe and feasible, the complete benefit is yet to be appreciated. At the present time, the two indications for which IRE has been selectively employed include locally advanced pancreatic cancer (Stage III) of the head or body/neck after induction chemotherapy (with or without chemoradiotherapy) either by itself or as an intraoperative adjunct to pancreatic resectional surgery [213] and in resections for borderline resectable cancers [214] where it may offer the benefit of margin accentuation. This benefit though is yet to be completely appreciated. It has been shown to offer a superior advantage in terms of survival in locally advanced pancreatic cancer when the data was compared to published data of patients treated with only chemotherapy and/or radiotherapy [213].

16.4.7 Fast-Track Protocols/Enhanced Recovery

Spurred on by the success of evidence-based clinical pathways in other surgical specialties such as colorectal and vascular surgery in enhancing perioperative patient experience and outcomes, ERAS® has found its way into pancreatic surgery, too. The initial experience suggests that it has contributed to significantly reduced morbidity, in general, as well as no increase in readmission rates [208]. In the author's experience [209], clinical pathways help to significantly reduce the duration of hospital stay. However, uniform application of clinical pathways may not be feasible with the need to tailor them to specific groups of patients such as obese

patients and those with respiratory comorbidities [209]. The aspect of ERAS® will be covered in detail in the chapter on perioperative patient care.

16.4.8 Palliation in Advanced Pancreatic Cancer

Palliation as defined by O'Neill and Fallon [215] and later reaffirmed by Miner and colleagues [216] includes treatments in advanced cancer that help relieve symptoms and improve quality of life. In pancreatic and periampullary cancers, the symptoms that would need to be palliated include obstructive jaundice, uncontrolled vomiting from gastroduodenal obstruction and pain. Traditionally, the surgery performed in the case of a patient undergoing a laparotomy and found to have an inoperable tumour is the triple bypass surgery that includes a side-to-side or end-to-side choledochojejunostomy with a retrocolic, side-to-side gastrojejunostomy and a side-to-side jejuno-jejunostomy.

A recent multicentre study demonstrated that palliative surgeries are associated not only with increased morbidity but no difference in survival compared to aborted laparotomies [217]. The concern in this subset of patients is that mortality rates in actual practice may be as high as 2.4-fold compared to reported literature [218]. Further, complications following palliative surgeries have been shown to significantly impact long-term survival [219].

The alternatives to surgery are SEMS for biliary and gastroduodenal obstruction. SEMS have been shown to have a low morbidity and mortality (procedure-related as well as 30 days) as compared to surgery [220]. Lyons and colleagues [221] have demonstrated that neither were bypass surgeries associated with fewer invasive procedures or reduced number of inpatient hospital days prior to death when compared to SEMS.

Optimization of cancer staging by effective use of staging laparoscopy especially in patients with borderline resectable or locally advanced cancers, as well as reducing the time interval between imaging and the planned surgery (shown to be associated with an increased ability to pick up metastases) thereby avoiding non-beneficial laparotomies in pancreatic cancer [222], should be the aim of clinicians dealing with likely unresectable pancreatic and periampullary cancers.

In patients with metastatic disease, non-surgical modalities for palliation should preferentially be resorted to. In patients with locally advanced cancers with a good performance status (European Co-operative Oncology Group score of 0–2) in whom non-surgical methods of palliation have been attempted and have been unsuccessful, and/or in those who have received neoadjuvant therapy and on surgical exploration (with an aim for trial of resection) were found to harbour non-metastatic, but unresectable, disease, the available evidence supports the creation of a prophylactic gastrojejunostomy in the setting of an inoperable pancreatic or periampullary cancer irrespective of the presence of features of gastric outlet obstruction [223, 224]. The author would also advise the creation of a feeding jejunostomy in patients who undergo a triple bypass and who had features of gastroduodenal obstruction preoperatively. Such patients tend to have a persistence of these symptoms in the early post-operative course, and a feeding jejunostomy helps maintain an enteral portal of nutrition.

Deep boring pain radiating to the back is a sign of advanced pancreatic cancer and may be encountered in up to 70% of patients. The cause of pain is multifactorial and has been hypothesized to be due to pancreatic ductal obstruction and resultant hypertension, neural (celiac plexus) invasion and the invasion of surrounding structures [225]. While treatment with non-steroidal anti-inflammatory drugs and opioids (working up the World Health Organization ladder) is useful in the initial management of pain, celiac plexus block performed either through image guidance, through endoscopic ultrasonography or at the time of palliative surgical exploration affords the best relief of pain. Although these patients may experience local pain, diarrhoea and hypotension on account of the celiac plexus block, these symptoms are transient. On the flipside, these patients required significantly less narcotic analgesics with a consequent reduction in the attendant side effects (constipation) [226].

16.4.9 Chemotherapy and Chemoradiotherapy for Pancreatic Cancer

16.4.9.1 Adjuvant Therapy

There have been eight randomized controlled trials that have examined the role of adjuvant chemotherapy and/or chemoradiotherapy in patients with resectable pancreatic cancer [227–236]. Table 16.6 provides an overview of these trials. The evidence clearly supports a survival advantage with adjuvant therapy. While three trials demonstrated a benefit of adjuvant chemotherapy (5-fluorouracil or gemcitabine) in terms of overall survival [227, 229, 230], two trials indicated a benefit of chemoradiotherapy [228, 233]. The ESPAC-1 trial, however, determined that only adjuvant chemotherapy and not chemoradiotherapy is associated with a significant survival benefit [230]. While single-agent gemcitabine has been the preferred drug in the adjuvant setting [237], the most recent trial from Japan [235] has demonstrated a significant survival advantage for S-1 (tegafur) over gemcitabine. These results need to be validated outside of Japan. The results from the 30.5 month median follow up of the PRODIGE24 trial (238) were recently presented. For patients aged 18–79 years, 21–84 days after R0 or R1 resection, WHO Performance status ≤1, adequate hematologic and renal function, and no cardiac ischaemia, mFOLFIRINOX has not only been shown to be safe, but associated with a significantly better disease-free and overall survival compared to Gemcitabine.

16.4.9.2 Neoadjuvant Therapy

Neoadjuvant therapy, chemotherapy with or without radiotherapy, is being considered in pancreatic cancer in two specific scenarios, namely, locally advanced or borderline resectable cancers with the aim of tumour downstaging [238] and tumour downsizing so as to increase the proportion of margin-negative resections [152], and in resectable cancers on the premise that pancreatic cancer is a systemic disease at the time of diagnosis [239, 240] and thus neoadjuvant therapy will help the tumour to declare its biology enabling surgical resections to be reserved for patients who would truly benefit from them [180, 241].

Table 16.6 Overview of the major randomized controlled trials exploring the role of adjuvant therapy in pancreatic cancer (updated from Shrikhande and Barreto [236]) [227–235] (Reproduced with permission from Elsevier)

Author	Trial name (year)	Comparative groups (*n*)	Median survival (months)	Conclusions
Kaiser and Ellenberg	GITSG (1985)	Surgery alone (22)	11	Adjuvant therapy may prolong
		Sx + 5-FU + RT (21)	20	Survival
Klinkenbijl et al.	EORTC (1999)	Sx alone (103)	19	Adjuvant chemo-RT is safe and well tolerated with no significant benefit
		Sx + 5-FU + RT (104)	24.5	
Neoptolemos et al.	ESPAC-1 (2004)	Surgery alone (69)	16.9	Adjuvant chemotherapy, but not chemo-RT, has a significant survival benefit
		Sx + 5-FU + RT (73)	13.9	
		Sx + 5-FU/leucovorin (75)	21.6	
		Sx + Chemo + RT + chemotherapy (72)	19.9	
Oettle et al.	CONKO-001 (2007) (2013)	Sx alone (175)	20.2	Following macroscopic complete removal of pancreatic cancer, adjuvant Gem (6 months) resulted in increased DFS and OS
		Sx + Gem (179)	22.8	
Regine et al.	RTOG 9704 (2008)	Sx + Gem + 5-FU/ EBRT + Gem (221)	20.5	Addition of gemcitabine to adjuvant fluorouracil-based chemo-RT is associated with a significant survival benefit
		Sx + 5-FU + 5-FU/ EBRT +5-FU (230)	16.9	
Ueno et al.	JSAP 02 (2009)	Sx alone (60)	22.3	Adjuvant Gem affords a significant improvement in DFS but does not influence OS
		Sx + Gem (58)	18.4	
Neoptolemos et al.	ESPAC-3 (2010)	Sx + 5-FU/leucovorin (551)	23	Adjuvant Gem offers no significant benefit as compared to 5-FU
		Sx + Gem (537)	23.6	
Uesaka et al.	JASPAC 01 (2016)	Sx + Gem (190)	25.5	Adjuvant S-1 offers a significant benefit as compared to Gem
		Sx + S-1 (187)	46.5	

Sx surgery, *S-1* tegafur (oral prodrug of 5-FU), *5-FU* 5-fluorouracil, *Gem* gemcitabine, *NCICCTG* National Cancer Institute of Canada Clinical Trials Group, *DFS* disease-free survival, *OS* overall survival, *QoL* quality of life, *FOLFIRINOX* 5-FU + oxaliplatin + irinotecan + leucovorin

While radiotherapy has been suggested to improve resection rates in locally advanced pancreatic cancer when combined with chemotherapy, the most encouraging results have been obtained with FOLFIRINOX-based therapy [238]. A recent study has reported a 60% resectability rate with FOLFIRINOX that was better than gemcitabine in combination with radiation therapy (46%) [242]. Downstaging with radiotherapy

occurs in less than one-third of patients [243]. Radiation (hypofractionated or conventional) has been shown to actually improve local control without impacting survival [244]. Neoadjuvant therapy does not appear to alter tumour biology [178]. Moreover, radiological restaging of tumours post-neoadjuvant therapy is still a challenge [179]. Whether neoadjuvant therapy actually increases margin-negative resections remains yet to be determined [245]. The PREOPANC trial [246] comparing preoperative chemoradiotherapy versus upfront surgery for resectable and borderline resectable tumours will certainly provide a clearer insight into whether neoadjuvant chemoradiotherapy alters survival, R0 resection rates, disease-free survival, etc.

In retrospective cohort series, survival rates following neoadjuvant therapy are best in patients who undergo a complete (R0) resection [247], who complete the therapy [152] and in those who have an increased histopathologic response [248]. Additionally, neoadjuvant therapy does not appear to influence post-surgical outcomes (morbidity and mortality) [249] and thus presents itself as a promising strategy in pancreatic cancer.

16.4.10 Metastatic Pancreatic Cancer

For decades, metastatic pancreatic cancer was regarded as chemotherapy-resistant. The first trial that heralded the role of gemcitabine as a single-agent monotherapy for palliation was conducted by Burris and colleagues [250]. Table 16.7 provides an

Table 16.7 Overview of the major randomized controlled trials exploring the role of chemotherapy in the palliation of metastatic pancreatic cancer [8, 9, 250–252]

Author	Trial name (year)	Comparative groups (*n*)	Median survival (months)	Conclusions
Burris et al.	– (1997)	Pain stabilization followed by:		Significantly better: (a) Clinical benefit response (b) Median survival (c) Survival at 12 months
		Gem (63)	5.65	
		5-FU (63)	4.41	
Moore et al.	NCICCTG (2007)	Gem + erlotinib (285)	6.24	First RCT to demonstrate a survival advantage by adding an agent to Gem
		Gem + placebo (284)	5.91	
Conroy et al. Gourgou-Bougade et al.	PRODIGE 4/ ACCORD 11 (2011)	FOLFIRINOX (171)	11.1	Significant survival advantage and reduced QoL impairment with increased toxicity
		Gem (171)	6.8	
Von Hoff et al.	MPACT (2013)	Nab-paclitaxel+		Significant improvement in OS, PFS and response rate with the addition of nab-paclitaxel
		Gem (431)	8.5	
		Gem (430)	6.7	

5-FU 5-fluorouracil, *Gem* gemcitabine, *NCICCTG* National Cancer Institute of Canada Clinical Trials Group, *PFS* progression-free survival, *OS* overall survival, *QoL* quality of life, *FOLFIRINOX* 5-FU + oxaliplatin + irinotecan + leucovorin

overview of the sentinel randomized (phase III) trials in metastatic pancreatic cancer [8, 9, 250–252]. The PRODIGE 4/ACCORD 11 trial [8] was not only the first trial to demonstrate an advantage of FOLFIRINOX over gemcitabine; the regimen was also found to be more cost-effective [253]. Ultimately, the choice of chemotherapy in this subset of patients would be between FOLFIRINOX (with its attendant better survival profile) and gemcitabine with nab-paclitaxel (with its better toxicity profile).

16.5 Future Research

There is a need for randomized trials to truly determine if M1 resections confer a survival benefit in pancreatic or periampullary cancers. Within the current realms of evidence, such studies must be undertaken preferably in high-volume centres and with all patients receiving chemotherapy first followed by randomization to either surgery and further therapy or chemotherapy alone.

There is a need for high-quality level 1 evidence to ascertain whether patients with borderline resectable cancers should undergo upfront surgery or surgery following neoadjuvant therapy. The impact of either therapy on overall survival needs to be determined within the context of a trial strictly adhering to the current definition of borderline resectable disease.

The benefit of procedures such as IRE in accentuating surgical resection margins in borderline and locally advanced pancreatic cancer needs to be tested within the confines of a clinical trial.

Whether genetic markers such as SMAD4 inactivation (predictive of early metastases [88]) will help in further selecting patients for such resections needs to be determined.

16.6 Summary

The overbearing nihilism in our perception of pancreatic cancer is preventing us from appreciating the small, but certain, advances in the management of this cancer. Periampullary cancer, on the other hand, remains a less investigated entity possibly due to its early presentation and hence relatively better outcomes as compared to pancreatic cancer. Scientifically tempered surgical aggression aimed at complete surgical resection coupled with the use of adjuvant chemo- or chemoradiotherapy (when indicated) offers the best possible outcome in patients with resectable or locally advanced but resectable disease. Data on the role of neoadjuvant chemotherapy in borderline resectable is encouraging, and this deserves further attention. Palliative surgery may yet possess a valuable role in pancreatic cancer in terms of improving quality of life coupled with gemcitabine-based mono- or combination therapies.

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