Multimodality Management of Borderline Resectable Pancreatic Cancer

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Preface

Over the past decade, great efforts have been made toward refining the clinical systems used to stage localized pancreatic cancer. As the benefits of the administration of preoperative therapy have increasingly become recognized, and as the performance of vascular resection and reconstruction at pancreatectomy has concurrently become more common, many infiltrative cancers that were historically considered unresectable are now more commonly described as "borderline resectable." Tumors in this category are those that are technically removable, but which are associated with a significant likelihood of a positive margin when surgery is performed de novo. Given that the overall survival rate of patients who undergo margin-positive operations is similar to that of patients who do not undergo surgery at all, recognition of borderline resectable pancreatic cancer as a unique clinical entity is critical, both for optimal patient care and for the proper evaluation of novel (neo) adjuvant treatment regimens in clinical trials.

In this book, we have assembled an internationally recognized group of clinical experts to compile an up-to-date appraisal of the diagnostic and therapeutic modalities used for patients with borderline resectable pancreatic cancer. The book includes an overview of clinical staging, a review of endoscopic approaches, a summary on the latest clinical research, and a discussion of emerging targeted therapies. We also present several well-illustrated surgical chapters on novel technical strategies and techniques that may be utilized to safely manage this difficult group of patients in the operating room.

We acknowledge Mr. Andy Kwan, Mr. Brian Halm, and Ms. Portia Wong from Springer, whose support of this project was essential for its development and completion.

We would like to thank the physicians who trained us to provide safe, thoughtful, and effective surgical care for patients with pancreatic tumors: Drs. Douglas Evans, Jeffrey Lee, Jason Fleming, Peter Pisters, Michael Bouvet, Andy Lowy, Jeffrey Matthews, Michael Edwards, and the late A.R. Moossa. We would also like to thank our families for their patience during the preparation of this book. Dr. Ahmad would like to acknowledge his wife, Shagufa, and his children, Samar, Ameen, and Saher. Dr. Katz would like to acknowledge his wife, Kristen, and children, Annie and Lucy.

Finally, we would like to dedicate this book to the patients and families who have battled pancreatic cancer. It is their courage and bravery that motivate and inspire us on a daily basis.

Houston, TX — Matthew H.G. Katz
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Part 1

Overview

Anatomic Definitions of Borderline Resectable Pancreatic Cancer

1

Rebecca A. Snyder, Alexander A. Parikh, Kamran Idrees, and Nipun B. Merchant

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States [1]. Although the incidence of pancreatic adenocarcinoma is lower than that of other malignancies, mortality rates remain high. In 2014, there were approximately 46,420 new cases of pancreas cancer and 39,590 people died of the disease [2]. The majority of patients present with advanced disease at the time of initial diagnosis; 5-year survival rates are estimated to be 9.9 % in patients with regionally advanced cancers and 2.3 % in those with distant disease [2]. Survival rates are higher for patients with localized tumors (25.8 %); however, fewer than 10 % of patients with pancreatic adenocarcinoma present at an early stage [2].

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As with other cancers, surgery offers the only opportunity for cure. Therefore, one of the most important determinants of overall prognosis for patients with pancreatic cancer is resectability. Indeed, a margin-negative resection is considered one of the strongest prognostic factors for long-term survival in patients with pancreatic cancer. Resection margins are classified as having no evidence of microscopic tumor deposits at or within 1 mm of the inked margins (R0) or as having microscopic tumor deposits but no gross tumor at the margins (R1). Discrimination between R0 and R1 margins is made on the basis of observations made by both the surgeon and the pathologist. Grossly positive resections (R2), which are now rare due to advances in preoperative staging, usually occur as a result of perineural or lymphatic invasion at the retroperitoneal margin within the neural plexus surrounding the SMA.

A number of studies have demonstrated that the median survival of patients who undergo margin-negative (R0) resection is significantly better (17–26 months) than that of patients who undergo a margin-positive (R1 or R2) resection (8–12 months) [3–9]. In fact, the median overall survival duration of patients who undergo R2 resection is no different than that of patients with locally advanced disease who are treated with palliative chemotherapy and/or chemoradiation. This fact emphasizes the critical need to determine each patient's likelihood of undergoing a margin-negative resection early in the development of the

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treatment plan [4, 6, 10, 11]. Unfortunately, fewer than 20 % of patients with pancreatic cancer present with disease amenable to R0 resection.

Historically, surgeons determined whether or not a patient had resectable cancer in the operating room at the time of laparotomy. In patients without evidence of liver or peritoneal metastases, division of the pancreas and stomach was performed to determine the relationship of a tumor within the pancreatic head or uncinate process to the mesenteric vessels. Over time, improvements in imaging capabilities, including computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), has allowed clinicians to better determine a patient's candidacy for a margin-negative resection *preoperatively*. At present, a triple-phase contrasted CT with thin cross-sectional cuts (≤3 mm) and sagittal and coronal reconstructions is the best preoperative imaging modality to characterize a patient's tumor, specifically with regard to its relationship to the surrounding vascular structures.

In the past, patients were considered to have resectable disease if the tumor had no direct contact with the celiac axis, hepatic artery (HA), superior mesenteric artery (SMA), superior mesenteric vein (SMV), or portal vein (PV). Radiographic tumor involvement of these vessels, in any capacity, was considered to represent locally advanced and unresectable cancer, as it was thought that a negative margin resection was not feasible in the setting of tumor involvement of the major mesenteric vasculature. However, patients whose tumors involve the SMV/PV and who receive modern multidisciplinary treatment regimens including pancreatectomy with concomitant vascular resection have a similar outcome to patients who do not require venous resection and reconstruction at the time of surgery [12–15]. Survival following pancreatectomy with concomitant resection of major arteries, on the other hand, is less encouraging. Although survival following pancreatectomy with concomitant arterial resection can be associated with reasonable rates of survival in highly selected patients, such operations are typically associated with prohibitive rates of perioperative morbidity and mortality [16–18].

Additionally, tumors with vascular involvement have historically been considered to have a fundamentally aggressive disease biology irrespective of treatment. For this reason, too, patients with tumors that involved major vascular structures were traditionally offered only palliative chemotherapy or chemoradiation therapy. With advances in systemic therapy, however, a subset of patients with historically unresectable tumors that have demonstrated an indolent disease process have been shown to benefit from surgical intervention.

These results have ultimately led to the development of the clinical stage of "borderline resectable" pancreatic cancer (BRPC). This stage designation categorizes a distinct subgroup of patients with localized tumors who are nonetheless at high risk for a margin-positive resection and early therapeutic failure when surgery is used as an initial treatment strategy. The administration of preoperative chemotherapy and/or chemoradiation therapy to patients with this stage of disease provides an opportunity for R0 resection. Furthermore, the administration of neoadjuvant therapy improves patient selection for surgery and helps surgeons avoid pancreatectomy for patients with biologically unfavorable disease.

Importance of a Definition

Because one of the critical determinations in the work-up of each patient with localized pancreatic cancer is the potential of undergoing a R0 resection, localized pancreatic tumors are generally divided on the basis of CT images into three clinical stages: resectable, borderline resectable, and locally advanced. Use of these descriptors—and specifically the use of the borderline resectable category—is helpful not only to understand a patient's prognosis, but also to determine the best treatment algorithm. Given their high likelihood of treatment failure with a surgery-first approach, patients with BRPC—in contrast to patients with resectable tumors—may benefit from multimodality therapy prior to intended resection.

One of the difficulties in attempting to precisely define BRPC is that the definition of what

constitutes a tumor in which an R0 resection can be achieved is highly variable and subjective amongst surgeons. In addition, clinical trials that have attempted to study BRPC have included patients with locally advanced disease, making not only defining BRPC challenging, but also making the interpretation of overall prognosis and treatment options very difficult. Only one multi-institutional prospective trial has been attempted to specifically study patients with BRPC; however, it closed prematurely from a lack of accrual due to a poorly defined study population that included patients with BRPC and locally advanced disease, and a lack of therapeutic and surgical standards [19]. A more standardized definition is clearly needed to allow accurate and meaningful investigation of the clinical management of this subset of patients.

Borderline Resectable Disease and Staging

Contemporary clinical staging for pancreatic cancer is outlined by the American Joint Committee on Cancer (AJCC) 7th edition using the TNM format. However, the subgroup of borderline resectable tumors is not well delineated within the current AJCC staging system. In that system, the primary tumor (T) stage is determined by size and extension beyond the pancreas. T3 tumors are those that extend beyond the pancreas without involvement of the celiac axis or SMA. In contrast, T4 tumors involve the celiac axis or SMA. Stage III cancer comprises T4 tumors with or without lymph node (LN) metastases. Stage III is considered to represent locally advanced, unresectable disease. Based on this system, tumors with <180° CA or SMA involvement on imaging—which would typically be considered borderline resectable using modern clinical staging—would be classified as unresectable. AJCC staging is therefore of limited clinical relevance in this patient population.

Relevant Anatomy

The fundamental .anatomic relationships relevant to the clinical staging of tumors of the pancreatic head include those between the primary tumor and the common hepatic artery (CHA), the SMA; and the (SMV), portal vein (PV), and SMV–PV confluence. In addition, the relationship of the tumor to the inferior vena cava (IVC) is often considered. For tumors of the pancreatic neck and body, the relationships between the tumor and the celiac axis (CA) and aorta are also relevant.

In an attempt to gain some clarity toward defining which patients have resectable, borderline resectable, or locally advanced disease, several entities have provided definitions for these categories of patients including MD Anderson Cancer Center (MDACC), the National Commission on Cancer Network (NCCN), and a joint consensus statement issued by the AHPBA, SSO, and SSAT medical societies (Table 1.1).

Table 1.1 Resectable pancreatic cancer definitions

	MDACC	AHPBA/SSO/SSAT	NCCN
Celiac axis (CA)	No extension	Clear fat plane around CA	No contact
Common hepatic artery (CHA)	No extension	Clear fat plane around CHA	No contact
Superior mesenteric artery (SMA)	No extension; normal fat plane between tumor and SMA	Clear fat plane around SMA	No contact
Superior mesenteric vein-portal vein (SMV–PV) confluence	Abutment or encasement with patent vessels (no occlusion)	No abutment, distortion, tumor thrombus, or encasement	No contact OR ≤180° contact without vein contour irregularity

MDACC MD Anderson Cancer Center, *AHPBA/SSO/SSAT* Americas Hepato Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, *NCCN* National Comprehensive Cancer Network

Definitions of Resectable Disease

Uniformly, resectable disease includes tumors that do not appear to contact the CA, HA, SMA, or SMV given that a margin-negative resection can often be achieved without any prior therapy in patients with these tumors. More recently, several groups have also considered as resectable tumors with limited involvement of the SMV–PV confluence in which an R0 resection is still possible, albeit with vascular resection and reconstruction. For example, the definition used at MDACC considers tumors resectable if there is abutment of the SMV–PV with patent vessels (no occlusion) [20]. The NCCN definition also classifies as resectable any tumor with ≤180° contact of the SMV–PV but without any vein contour irregularity [21] (Table 1.1, Fig. 1.1).

Definitions of Locally Advanced Disease

Definitions of locally advanced disease (LAD) also vary, although in general, LAD characterizes those patients in whom the likelihood of response to non-operative therapy sufficient to allow for a subsequent margin-negative resection is nearly zero. For example, according to the MDACC definition, locally advanced disease consists of tumors that involve the SMA greater than 180°, those that encase the CA or CHA without a technical option for reconstruction, and those which occlude the SMV–PV with no technical option for reconstruction [20].

The NCCN considers tumors of the pancreatic head and uncinate process locally advanced if the tumor demonstrates contact with the first jejunal vein draining into the SMV or an unreconstructable SMV–PV confluence. Tumors with >180° contact with the SMA, CA, or contact the first jejunal arterial SMA branch are also considered locally advanced. Body and tail tumors are considered locally advanced if the SMV–PV confluence is involved and unreconstructable or if there is contact of >180° with the SMA or HA, or with the CA and aorta (Table 1.2, Figs. 1.2 and 1.3).

Definitions of Borderline Resectable Disease

The definition of borderline resectable (BRPC), first termed *marginally* resectable, was first described in 2001 in a prospective case series by Mehta et al. and was intended to describe patients

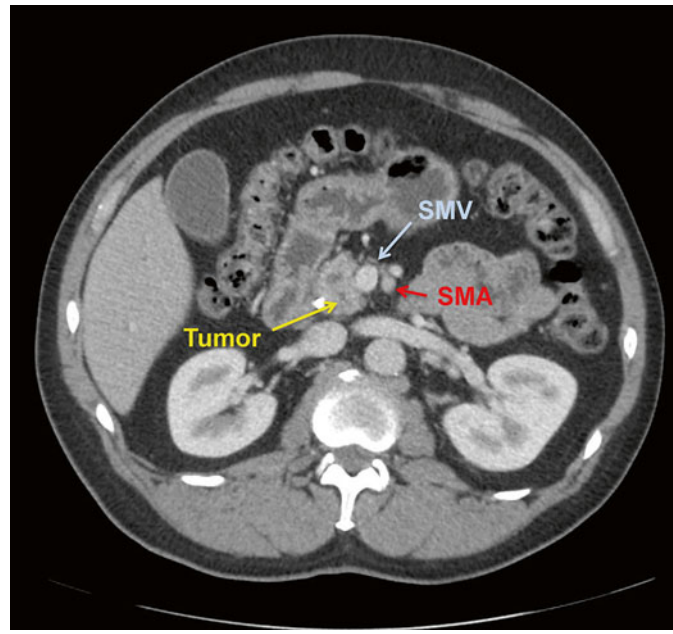

Fig. 1.1 CT scan demonstrating resectable pancreatic adenocarcinoma of the head with SMV abutment of less than 180° and a clear fat plane between the tumor and the SMA

Table 1.2 Locally advanced (unresectable) pancreatic cancer definitions

	MDACC	AHPBA/SSO/SSAT	NCCN
Celiac axis (CA)	Encasement	Abutment or encasement	Contact >180°
Common hepatic artery (CHA)	Encasement with no technical option for reconstruction	Encasement with extension to celiac axis	Contact with extension to CA or bifurcation
Superior mesenteric artery (SMA)	Encasement >180°	Encasement >180°	Contact >180° or contact with first jejunal SMA branch
Superior mesenteric vein-portal vein (SMV–PV) confluence	Occluded and no technical option for reconstruction	Occlusion without options for reconstruction	Unreconstructible due to tumor involvement or occlusion, contact with proximal jejunal branch

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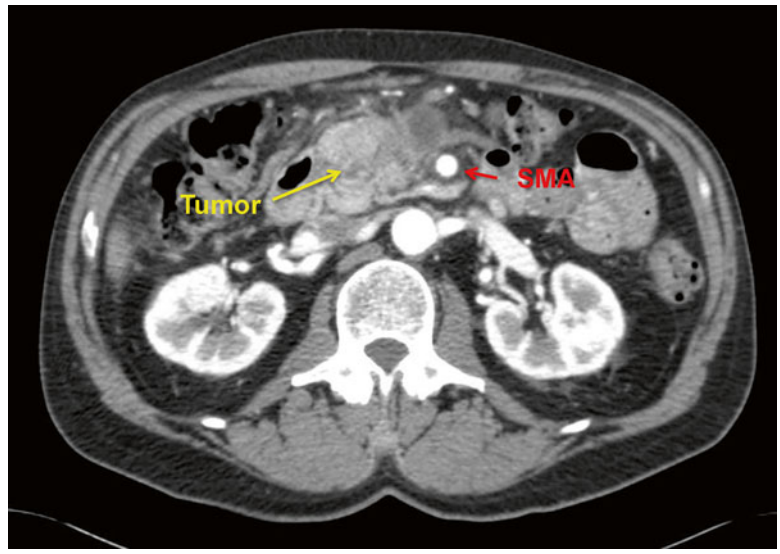

Fig. 1.2 CT scan of a locally advanced pancreatic adenocarcinoma with obliteration of the SMV at the base of the mesentery, leaving no distal venous target for reconstruction

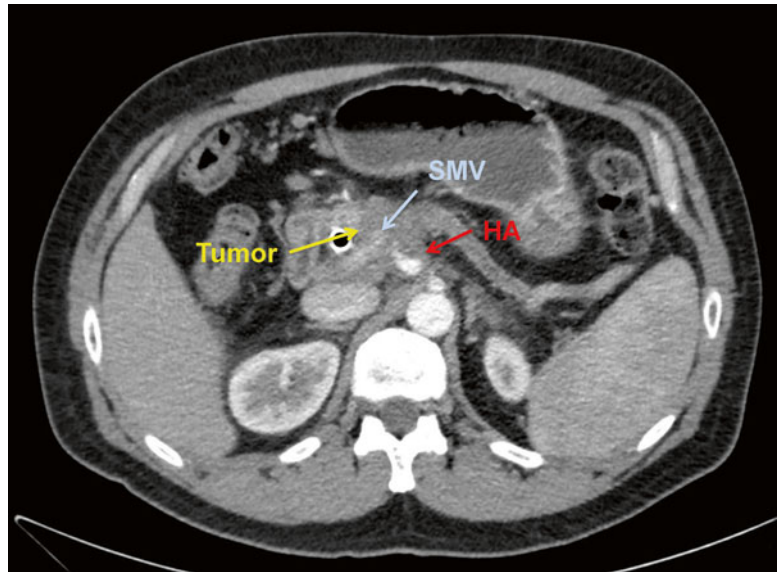

Fig. 1.3 CT scan of a locally advanced pancreatic adenocarcinoma with encasement of the SMV as well as the CHA (common hepatic artery)

at high risk of grossly positive margins with immediate resection [22]. Patients were treated with 5-FU and radiation therapy and then re-evaluated for resection; 9 of 15 patients subsequently underwent resection with negative margins [22]. In 2006, the NCCN first adopted the term "borderline resectable" to characterize the group of patients at high risk for a margin-positive resection and for whom administration of neoadjuvant therapy should be considered.

Over the past decade, a number of different radiographic classification schemes have been subsequently developed to describe which patients are considered borderline resectable, including consensus statements and guidelines from not only the NCCN, but also the International Study Group of Pancreatic Surgery (ISGPS); MDACC; Americas Hepato Pancreato-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), and Society for Surgery of the Alimentary Tract (SSAT) [20, 23, 24]. A definition has also been established within the context of a now-completed multi-institutional prospective trial, the Intergroup borderline resectable pilot study (Alliance A021101) [25]. These criteria have been endorsed by the NCCN and are summarized in Table 1.3 and shown with representative CT scans in Figs. 1.4, 1.5, and 1.6. To date, no single definition has been used uniformly.

The most recent NCCN guidelines outline a definition of BRPC as tumor demonstrating radiographic contact with the SMV–PV of >180°, or contact of ≤180° with contour irregularity or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement to allow for adequate resection [21]. Solid tumor contact with the IVC is also considered borderline resectable. Regarding arterial involvement, NCCN considers tumor contact with CHA without extension to CA or HA bifurcation and ≤180° contact with SMA to be borderline resectable for pancreatic head lesions. A tumor within the body or tail is considered borderline resectable if there is contact ≤180° with CA or >180° of CA without involvement of aorta and with an uninvolved, intact GDA.

The MDACC definition published in 2006 allows for short segment occlusion of the SMV–PV as long as a suitable vessel is available above and below the involved segment for reconstruction [20]. Additionally, tumor abutment of ≤180° of the circumference of the SMA and short segment encasement or abutment of the CHA (usually at the GDA origin) is considered potentially resectable. In follow-up work, Katz et al. elaborated on these definitions further, to not only account for anatomical feasibility but also clinical appropriateness for pancreatectomy [26]. MDACC categorized patients into three subsets: Group A comprised patients meeting the anatomic criteria listed above; Group B consisted of patients with preoperative work-up suggestive but not diagnostic of metastasis; and Group C was made up of patients with comorbidities or those with a marginal, but potentially reversible, performance status (typically ECOG 2-3). Group B patients had CT findings suspicious for but not diagnostic of metastatic disease (indeterminate subcentimeter liver lesions or peritoneal or omental nodules too small for biopsy) or known N1 disease as determined by EUS-FNA or pre-referral laparotomy.

In 2008, the AHPBA, SSO, and SSAT held a Consensus Conference to outline a uniform definition of borderline resectable disease [25]. Published in 2009, the proceedings delineated the following criteria to define BRPC: tumor-associated deformity of the SMV–PV, abutment of the SMV–PV ≥180°, short-segment occlusion of the SMV–PV amenable to resection and reconstruction, short-segment involvement of the HA or its branches amenable to resection and reconstruction, and abutment of the SMA (<180°).

The ISGPS published a consensus statement in 2014 intended to promote an internationally agreed upon definition for the subset of patients with BRPC [24]. This group endorses the NCCN criteria for the definition, based on preoperative CT imaging performed within 4 weeks of consideration for resection. Consistent with NCCN, the ISGPS classification of BRPC allows for SMV–PV occlusion if reconstruction is possible, encasement of the GDA up to the HA with encasement of HA without extension to the CA, and abutment of the SMA <180°.

Most recently, members of several cooperative groups, including the Southwest Oncology

Table 1.3 Borderline resectable pancreatic cancer definitions

	MDACC	AHPBA/SSO/SSAT	NCCN/ISGPS	Moffitt	Intergroup (Alliance A021101)
Celiac axis (CA)	Abutment	No abutment or encasement	Contact ≤180° or contact >180° with uninvolved GDA	Not specified	Interface between tumor and vessel <180° circumference vessel wall
Common hepatic artery (CHA)	Abutment or short segment encasement	Short segment abutment or encasement amenable to reconstruction	GDA encasement to hepatic artery with short segment encasement or direct abutment without extension to hepatic bifurcation or celiac axis	Encasement of GDA up to origin of CHA	Reconstructible, short-segment interface between tumor and vessel of any degree
Superior mesenteric artery (SMA)	Abutment <180°	Abutment <180°	Contact ≤180°	Circumferential tumor abutment <180°	Interface between tumor and vessel measuring <180° circumference of vessel wall
Superior mesenteric vein-portal vein (SMV–PV) confluence	Short segment occlusion amenable to resection and reconstruction	Abutment >180° or occlusion amenable to resection and reconstruction	Contact of >180°, contact of ≤180° with irregularity of vein or thrombosis amenable to resection and reconstruction	Circumferential abutment or encasement amenable to resection and reconstruction	Interface between tumor and vessel measuring 180° or greater of circumference of vessel wall, and/or reconstructable occlusion

MDACC MD Anderson Cancer Center, *AHPBA/SSO/SSAT* Americas Hepato Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract, *NCCN* National Comprehensive Cancer Network, *ISGPS* International Study Group of Pancreatic Surgeons

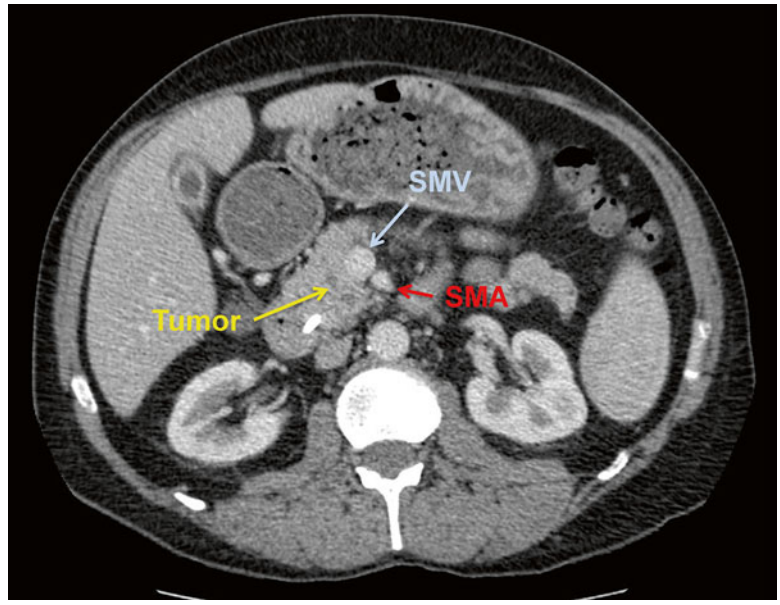

Fig. 1.4 CT scan demonstrating a borderline resectable pancreatic adenocarcinoma with SMV abutment of approximately 180° and subtle haziness posterior to the SMA

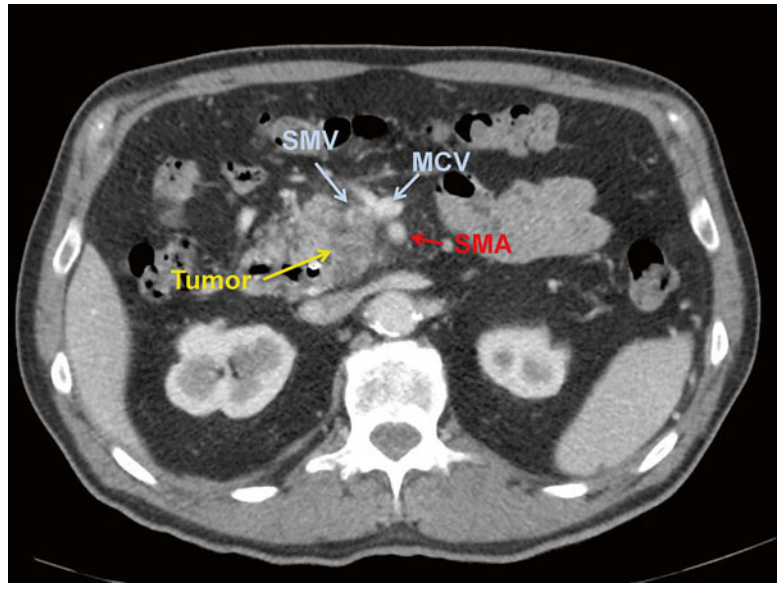

Fig. 1.5 CT scan demonstrating a borderline resectable pancreatic adenocarcinoma with tumor thrombus within the SMV

Group, (SWOG) Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group (ECOG), and Radiation Therapy Oncology Group (RTOG), proposed a precise definition for use in a now-completed pilot study for patients with BRPC. The Alliance Trial (A021101) was a multi-institutional single-armed trial designed to evaluate the feasibility of multi-institutional study of BRPC using a modified regimen of FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and 5-FU) followed by 5040 Gy external beam radiation therapy prior to intended surgery [26]. Here, the investigators advocated for an easily reproducible definition based on objective data derived from standard CT imaging and suggested avoidance of subjective or imprecise

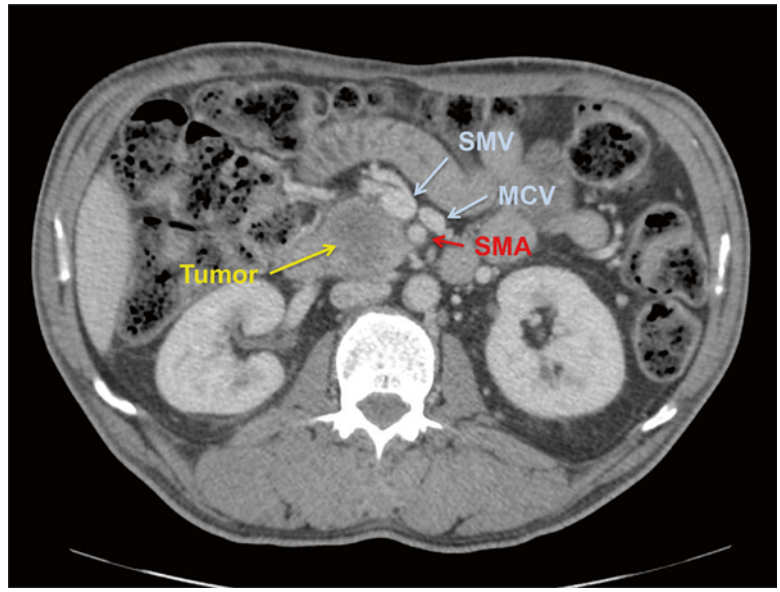

Fig. 1.6 CT scan demonstrating a borderline resectable pancreatic adenocarcinoma with SMV abutment of approximately 180° at the base of the mesentery and haziness around the SMA

assessments of "impingement" or "abutment." This definition consisted of the following: (1) an interface between the tumor and SMV–PV ≥180° of the vein wall circumference; (2) short-segment occlusion of the SMV–PV with normal vein above and below the obstruction amenable to resection and reconstruction; (3) short-segment interface of any degree between tumor and HA with normal artery proximal and distal to the interface amenable to arterial resection and reconstruction; and (4) interface between the SMA and CA measuring <180° of the circumference of the artery.

Classifying Venous Involvement

In addition to the definitions described above, there have been efforts to describe the extent of venous involvement based on preoperative imaging in order to more accurately predict the likelihood of R0 resection and define borderline resectable disease. In 1991, Ishikawa et al. published a classification system of SMV–PV involvement based on the portal phase of preoperative arteriography [27]. Invasion of the SMV–PV was classified as Type (I) normal, (II) smooth shift without narrowing, (III) unilateral narrowing, (IV) bilateral narrowing, (V) bilateral narrowing with the presence of collateral veins.

A follow-up study in 2010 at Fox Chase Cancer Center utilized the Ishikawa definitions to evaluate the effect of neoadjuvant chemoradiation therapy among patients with SMV–PV involvement [28]. Preoperative therapy was associated with improved R0 resection rates and overall survival among patients with Type II or III vein involvement, but not in patients with Type IV or V. However, the number of patients with bilateral involvement or occlusion (Type IV or V) was small.

More recently, Tran Cao et al. correlated preoperative CT imaging of the circumferential SMV–PV tumor-vein interface (TVI) with the presence of histologic vein invasion postresection in order to determine the ability of preoperative radiographic criteria to predict the need for vein resection at the time of pancreaticoduodenectomy [29]. The TVI was assigned to the following classifications: (1) No direct interface with either normal pancreas or fat separating the primary tumor from the vessel, (2) ≤180° of the vessel circumference, (3) >180° of the vessel circumference, or (4) vascular occlusion (absence of contrast within the lumen of the vein in association with adjacent tumor). Based on review of

254 patients undergoing pancreaticoduodenectomy, the authors found that the TVI system predicted the need for SMV–PV resection and histologic vein involvement with reasonable accuracy. Specifically, 89.5 % of patients with TVI >180° or occlusion required SMV–PV resection, and 82.4 % of these patients had documented histologic SMV–PV invasion.

Validation of Classification Systems

Although the various anatomic definitions are similar, there are several important differences among them. Unfortunately, it is very difficult to ascertain which definition is most appropriate without comparison or validation studies. Extrapolating from a number of single-institution, retrospective studies investigating neoadjuvant chemotherapy and/or chemoradiation therapy prior to resection in the borderline resectable population, it is possible to perform a limited comparison of resection rates by definition.

By definition, a proportion of patients with initially BRPC are expected to have disease progression, but an additional percentage will ultimately represent reasonable candidates for margin-negative resection. However, it is unclear as to what percent of patients that come to resection after neoadjuvant therapy should be considered the benchmark to validate a definition of BRPC.

Among recent studies using the NCCN consensus definition, resection rates range from 46 to 56 % after preoperative therapy [30, 31]. Rates of resection among patients considered to have borderline resectable disease based on the MD Anderson definition range between 18 and 46 % after completion of neoadjuvant therapy [26, 32, 33]. In a study comparing rates using both the AHPBA/SSO/SSAT definition and the MD Anderson definition among the same study population, resection rates differed significantly at 84 % and 78 %, respectively [34]. Given that the AHPBA/SSO/SSAT definition considers abutment or encasement of the SMV–PV to be BRPC, whereas MD Anderson considers those patients candidates for upfront resection, it is not surprising that resection rates differ. Additionally, MD Anderson definition allows for a greater extent of arterial involvement, specifically abutment of the celiac artery, compared to the AHPBA/SSO/SSAT definition.

Of equal importance, the neoadjuvant treatment regimens differed significantly across these studies which adds another significant confounder, further limiting comparisons of the various definitions.

Special Considerations: Aberrant Anatomy

As many as 40–45 % of patients have a variation in visceral arterial anatomy, which becomes an important consideration in the surgical evaluation of patients with pancreatic cancer [35]. The most common anomaly is a replaced or accessory right hepatic artery, originating off the SMA in approximately 11–15 % of patients. In this setting, the right HA courses posterior to the head of the pancreas and is positioned lateral to the PV, entering the right side of the hepatoduodenal ligament. Additionally, in approximately 2.5 % of patients, a replaced CHA can arise from the SMA and follow a similar path.

Although not specifically addressed in the contemporary definitions of BRPC, abutment or encasement of either a replaced (not accessory) right HA or replaced CHA should also be considered BRPC, consistent with borderline resectable definitions of CHA involvement.

Summary

The concept of BRPC is a relatively recent, but important development in the treatment of pancreatic cancer. The evolution of this category is two-fold. First, even with modern imaging techniques, a percentage of patients who undergo attempted resection will have microscopic residual disease left behind, primarily adjacent to the mesenteric vasculature. These patients, unfortunately, do not benefit from immediate resection and should be treated instead with systemic and/or

locoregional therapy prior to attempted resection. Second, largely due to advances in our understanding of the biology of the disease and to somewhat improved locoregional and systemic therapies, there appears to be a subset of patients whose tumors do not progress (or may even regress) following neoadjuvant therapy. These patients may represent suitable candidates for resection. These patients are considered to have borderline resectable tumors.

Although conceptually this definition appears fairly straightforward, the precise definition of BRPC remains somewhat subjective. While the various definitions have similar core components, differences exist regarding the precise details of vascular involvement. In addition, with significant institutional differences associated with the treatment of borderline resectable disease, a direct comparison amongst these definitions is nearly impossible. The recently completed Alliance pilot trial used a more objective definition of BRPC with attempted centralized review for rapid evaluation and consistency in a multicenter fashion. The pilot trial has recently been completed, and it is our hope that the success of this trial will pave the way not only for future studies in regard to the best treatment options, but also for a universal definition of BRPC.

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Part 2

Staging and Pretreatment Management

Imaging Evaluation of Borderline Pancreatic Cancer

2

Kyuran Ann Choe and Nicholas M. McDonald

Introduction

Pancreatic adenocarcinoma has been increasing in incidence [1] and it has been estimated to represent 3 % of new cancer diagnoses and 7 % of cancer deaths in 2014 [2]. Most commonly, the staging of pancreatic carcinoma follows American Joint Committee on Cancer (AJCC) guidelines. In the absence of metastatic disease, there is concurrent classification of tumors into resectable, borderline resectable, and unresectable locally advanced disease for the purposes of clinical management [3–6]. Although there is discussion regarding some of the criteria that define borderline resectable and locally advanced pancreatic cancer, both tumor staging and evaluation of local extent of disease for potential resectability are based on findings seen on cross-sectional imaging, primarily contrast-enhanced multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI).

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Ultrasound

Transabdominal ultrasound is frequently the initial examination that is performed in a patient with jaundice and it is sensitive for the detection of biliary ductal dilation. However, the etiology of the biliary obstruction can be difficult to elucidate and visualization of the entirety of the pancreas is difficult due to patient body habitus and interference from overlying bowel gas which limits tumor detection. In addition, when a tumor is present, complete assessment of local tumor extension is limited [7]. The finding of biliary and/or pancreatic ductal dilation on ultrasound commonly prompts further imaging evaluation by CT or MRI. The role of endoscopic ultrasound will be discussed in Chaps. 3 and 4.

Multidetector Computed Tomography

Optimal imaging of the abdomen and pelvis by CT for the evaluation of patients with pancreatic carcinoma is performed using multidetector scanners which provide thin slices and isotropic data for multiplanar reformatted images and 3D reconstructions. Rapid image acquisition allows for multiple phases of image acquisition with contrast enhancement optimized for tumor detection, vascular assessment, and evaluation for metastatic disease. Initial noncontrast imaging of the

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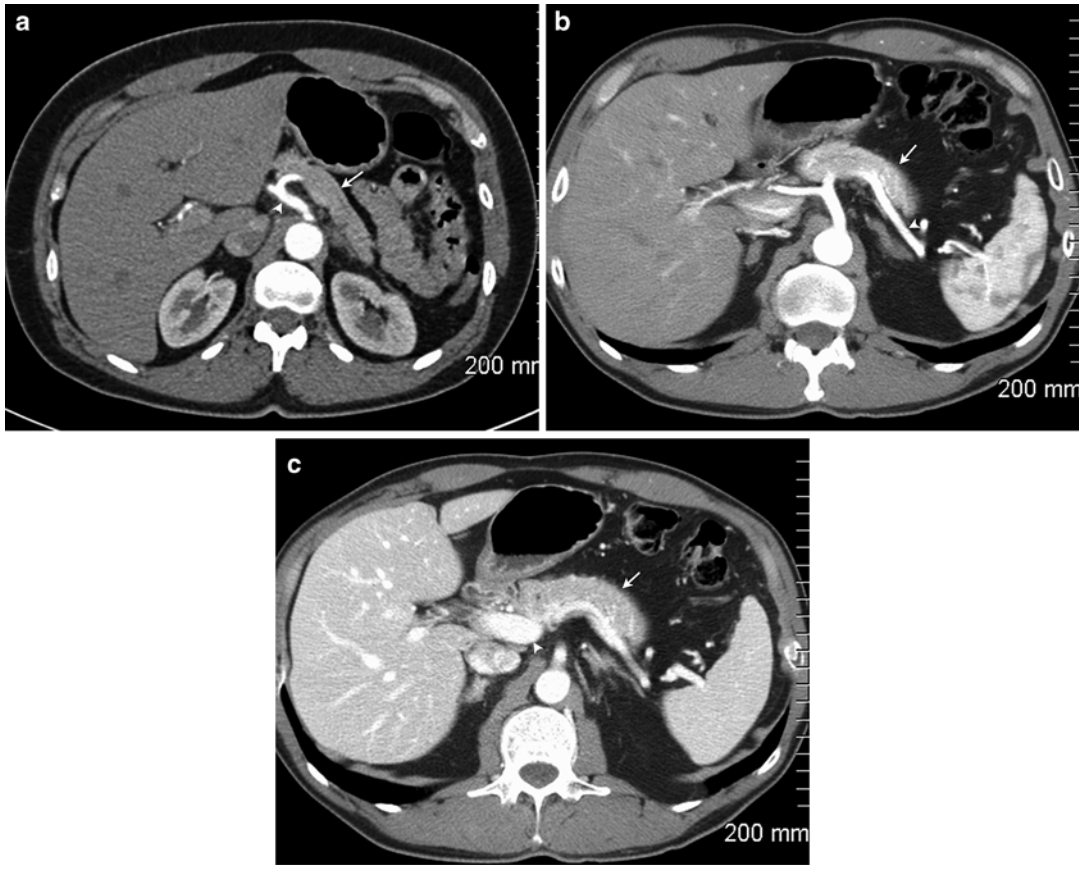

Fig. 2.1 Normal multiphasic appearance of the pancreas and adjacent structures. The arterial phase image (**a**) demonstrates dense arterial enhancement of the celiac artery (*arrowhead*) and mild enhancement of the pancreas (*arrow*). The pancreatic parenchymal phase (**b**) shows excellent arterial enhancement of the splenic artery (*arrowhead*) with enhancement of the pancreas (*arrow*). In the portal venous phase (**c**), there is dense enhancement of the portal vein (*arrowhead*) with persistent enhancement of the pancreas (*arrow*). There is parenchymal enhancement of the liver

abdomen is not required but is recommended in the 2012 National Comprehensive Cancer Network (NCCN) guidelines [8]. Negative enteric contrast (usually water) is used to avoid obscuration of the vasculature particularly if 3D reconstructions are utilized [9, 10]. Following intravenous high-iodine (>300 mg I/mL) contrast administration at 3–5 mL/s [11], images may be acquired in the angiographic arterial phase, pancreatic parenchymal phase [12], and portal venous (hepatic) phase (Fig. 2.1). Images are acquired in at least two of these phases, one of which is the portal venous (hepatic) phase for the detection of metastatic disease [13, 14]. At our institution, the portal venous phase extends through the pelvis to assess for metastatic disease if a recent CT has not been performed. The arterial angiographic phase (Fig. 2.1a) will optimally demonstrate the arteries with less background solid organ enhancement (for 3D volume rendered images), but has less sensitivity for lesion detection due to less image contrast between the tumor and normal parenchyma [13]. Some authors advocate image acquisition in the late arterial/pancreatic parenchymal phase (Fig. 2.1b) to optimize lesion detection and local arterial vascular involvement since the image contrast between the tumor and normal parenchyma is greater in this phase in addition to greater arterial enhancement [13, 15, 16]. The timing of image acquisition is dependent

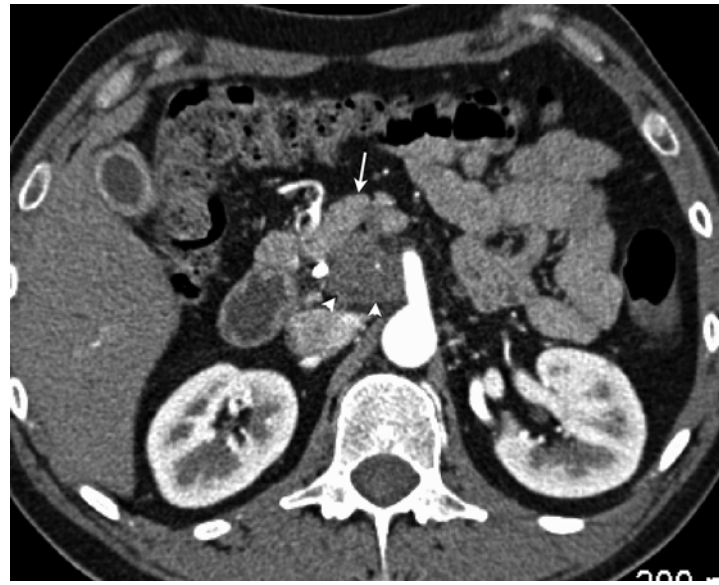

Fig. 2.2 Pancreatic adenocarcinoma in the uncinate process (*arrowhead*) appears hypodense in comparison to the normal parenchyma (*arrow*)

upon the rate of intravenous contrast administration which is 3–5 mL/s. The arterial phase of enhancement is at 30, 25, and 20 s following the start of peripheral intravenous contrast administration at an injection rate of 3, 4, and 5 mL/s, respectively [13]. Similarly, the normal pancreas demonstrates peak parenchymal enhancement at 50, 45, and 40 s, respectively [13]. Images in the portal venous phase are acquired between 60 and 70 s [13]. Images are typically reconstructed at slice thicknesses of 3 mm or less [3]. The thinner slice data (1.0 mm or less) is used for multiplanar and 3D reconstruction. If the initial examination is not of diagnostic quality to perform adequate tumor and vascular assessment, it should be repeated using a dedicated pancreas cancer protocol [11]. Preferably, imaging is performed prior to biliary stent placement since the stent may cause streak artifact at the level of the pancreatic head limiting evaluation of the local extent of tumor and secondary pancreatitis may obscure the primary lesion and complicate vascular assessment [3, 14].

Pancreatic adenocarcinoma is typically isodense to the normal pancreas on the noncontrast images, limiting their utility for the purposes of staging. Most pancreatic adenocarcinoma tumors enhance less than the normal pancreatic parenchyma and appear hypodense on contrast-enhanced images (Fig. 2.2). The sensitivity for the detection of tumor is greatest in the pancreatic parenchymal phase in comparison to the arterial and portal venous phases due to maximal differential enhancement and image contrast between tumor and normal parenchyma [13]. Isoattenuating and isoenhancing tumors (Fig. 2.3) comprise a small portion of tumors—5.4 % of pancreatic adenocarcinoma tumors evaluated in a recent study [17] and 11 % in an older study [18]. A higher percentage of smaller (2 cm or less) tumors have been shown to be isoattenuating [19]. These tumors are difficult to detect but may be inferred by secondary signs including mass effect of the tumor on the contour of the pancreas or on adjacent structures or by the level of biliary and/or pancreatic ductal obstruction [17, 18]. When tumors are isoattenuating, evaluation of local extent of disease can be difficult; particularly problematic is the assessment of abutment or encasement of the intrapancreatic portion of the portal vein and superior mesenteric vein in the absence of distortion.

Evaluation of the local extent of the tumor requires careful evaluation of the local vasculature, including the celiac artery and branches, superior mesenteric artery, superior mesenteric vein, and portal vein. Evaluation for aberrant vasculature such as a replaced or accessory right

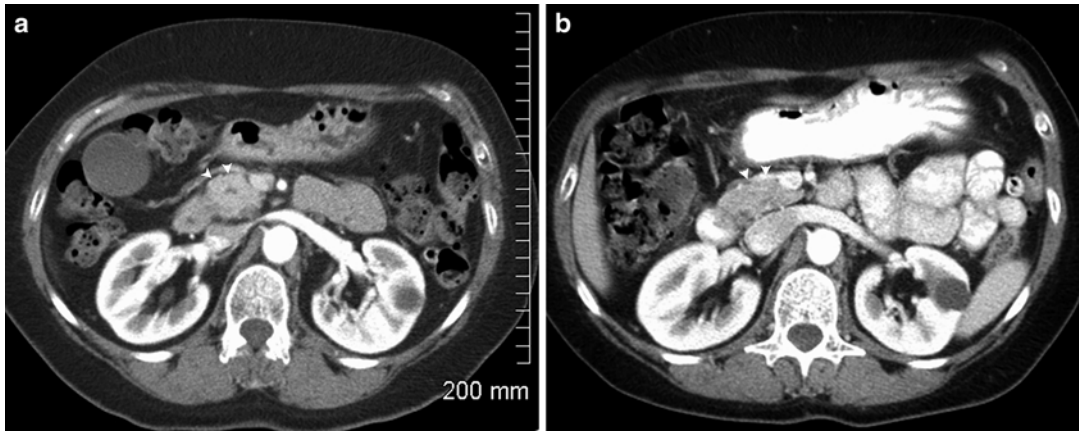

Fig. 2.3 Isodense pancreatic adenocarcinoma. A pancreatic head mass (*arrowhead*, **a**) is present causing a contour bulge anteriorly which was not present on a comparison CT (**b**). The central hypodensity seen in (**a**) is the pancreatic duct

hepatic artery or a replaced common hepatic artery originating from the superior mesenteric artery is also important as the course of these vessels frequently lies between the inferior vena cava and portal vein at the pancreatic head (Fig. 2.4). In the absence of distant metastases, preservation of the fat and soft tissue planes surrounding the adjacent vasculature indicates resectable disease (Fig. 2.5).

The delineation between resectable, borderline resectable, and unresectable locally advanced tumor is based upon the relationship between the tumor and adjacent vasculature [4–6]. Assessment of tumor involvement of the vasculature has been defined relative to the circumference of the vessel [20] without or with distortion of the vessel. An interface between the tumor and vessel of 180° or less has been termed abutment (Fig. 2.6) and greater than 180° has been termed encasement (Fig. 2.7) [11]. Greater than 180° of interface between tumor and vessel (encasement) was demonstrated to be specific for vessel invasion [20]. Irregularity of the vessel contour or narrowing (deformity) is also indicative of vascular invasion (Fig. 2.8) [11, 14]. Multiplanar reformatted images are beneficial for evaluation of the vessels with tumor involvement and assessment of degrees of the interface between the tumor and the vessel (Fig. 2.9) [15, 21, 22]. Vascular tumor obliteration or bland thrombus should also be noted. Since the definition of borderline resectable tumors includes those tumors where arterial or venous resection and reconstruction are being considered, assessment of longitudinal extent of tumor along the portal vein,

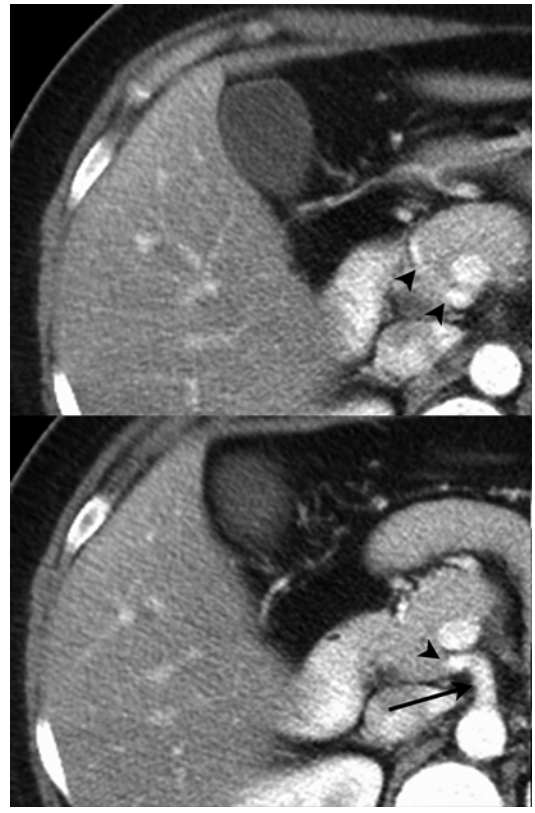

Fig. 2.4 Two adjacent slices demonstrate a replaced common hepatic artery (*arrowhead*) originating from the superior mesenteric artery (*arrow*)

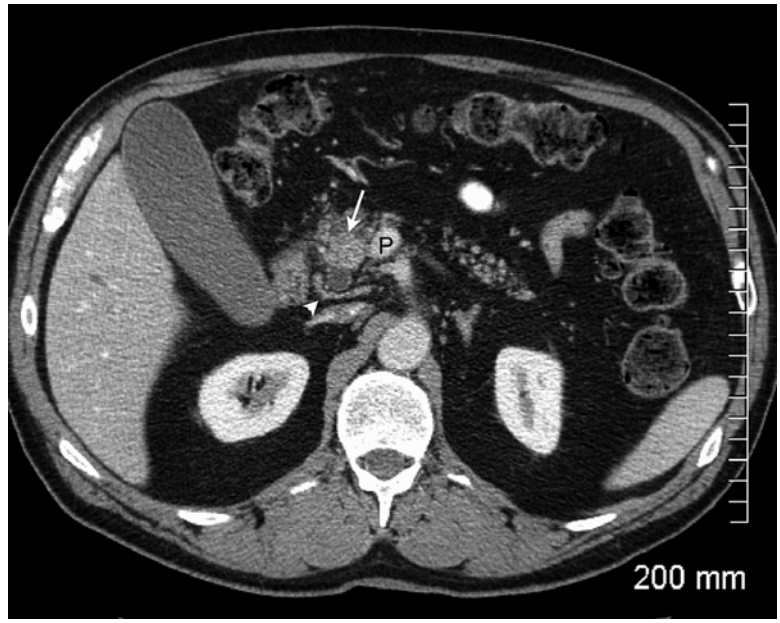

Fig. 2.5 The pancreatic head mass (*arrow*) appears relatively hyperdense due to fatty infiltration of the pancreas. A normal tissue plane is maintained between the tumor and the portal vein (*P*). There is a replaced right hepatic artery (*arrowhead*) seen posterior to the pancreatic head

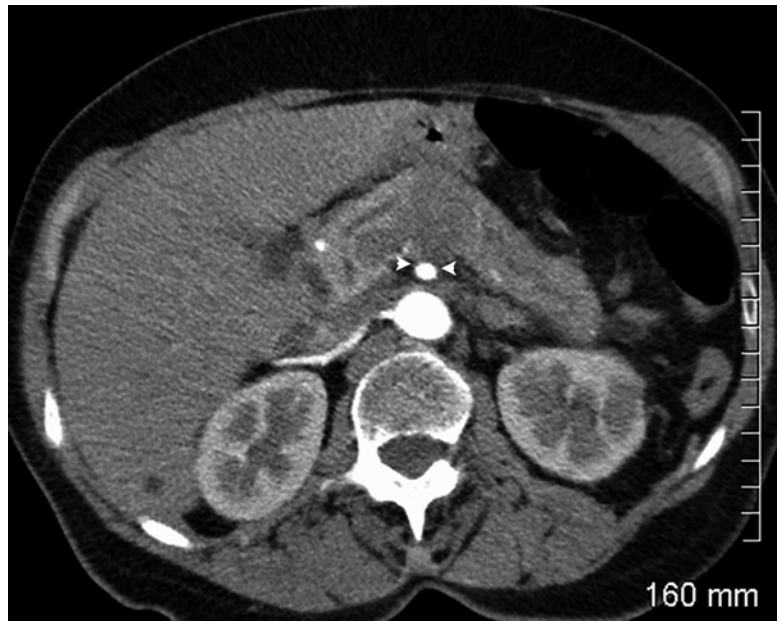

Fig. 2.6 The pancreatic mass abuts the superior mesenteric artery by about 120° (between *arrowheads*). The soft tissue seen posterior to the superior mesenteric artery is the left renal vein

superior mesenteric vein, and artery and hepatic artery should also be noted [3].

The definition of borderline resectable tumor is under some debate with at least three prevailing definitions, the AHPBA/SSO/SSAT consensus conference [6], the NCCN 2014 guidelines [4], and the Intergroup study [5]. The most recent 2014 NCCN guidelines acknowledge the need for more restrictive definitions of borderline resectable tumors in clinical trials [4].

Pancreatic adenocarcinoma may also directly extend to involve adjacent structures, including adjacent bowel, mesentery, spleen, kidneys, adrenal glands, aorta, and inferior vena cava (Fig. 2.10).

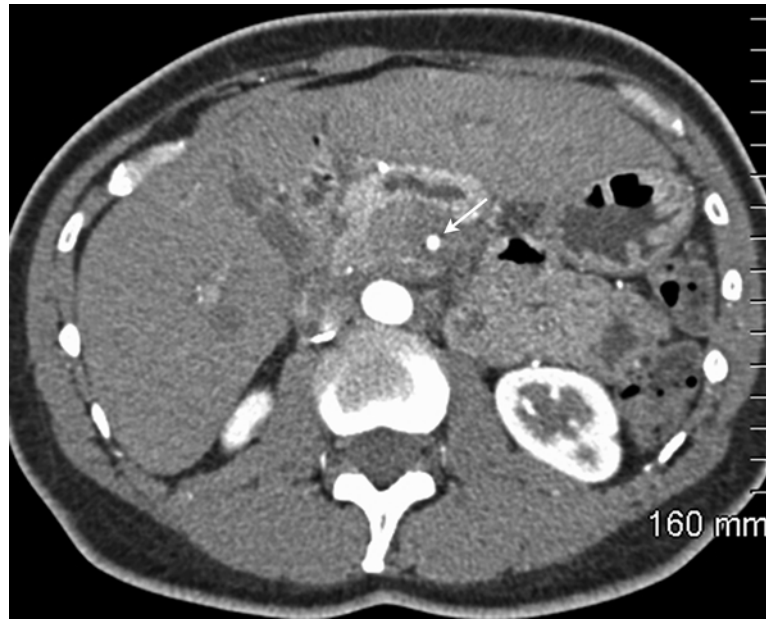

Fig. 2.7 Pancreatic adenocarcinoma circumferentially encases the superior mesenteric artery (*arrow*)

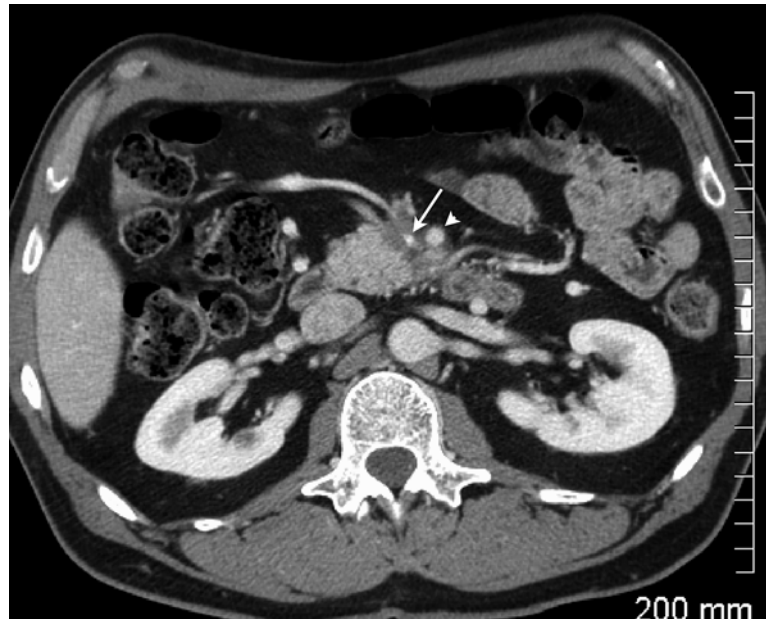

Fig. 2.8 Tumor is seen encasing and distorting the superior mesenteric vein (*arrow*). There is greater than 180° of encasement of the superior mesenteric artery (*arrowhead*)

Manifestations of metastatic disease include hepatic metastases, adenopathy beyond the local region, and peritoneal carcinomatosis. Hepatic metastases are typically hypovascular and are best visualized on portal venous phase imaging, appearing hypodense to the enhancing liver (Fig. 2.11). Small liver lesions can be particularly difficult to characterize [14]. Evaluation for adenopathy is based on size criteria (greater than 1 cm) and enlarged lymph nodes are particularly notable if outside the potential surgical resection bed. Peritoneal tumor may be seen as peritoneal nodularity, omental or serosal thickening or nodularity (Fig. 2.12). However, small volume metastatic deposits on or in the liver and small peritoneal implants are difficult to visualize by imaging [3, 23].

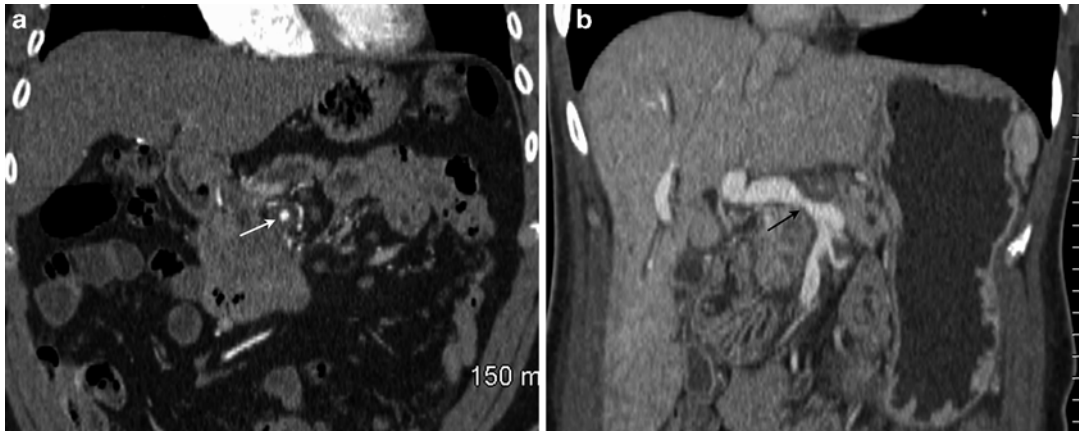

Fig. 2.9 Coronal multiplanar reformatted images demonstrate encasement of the superior mesenteric artery (**a**, *arrow*) and encasement with narrowing of the portal vein (**b**, *arrow*)

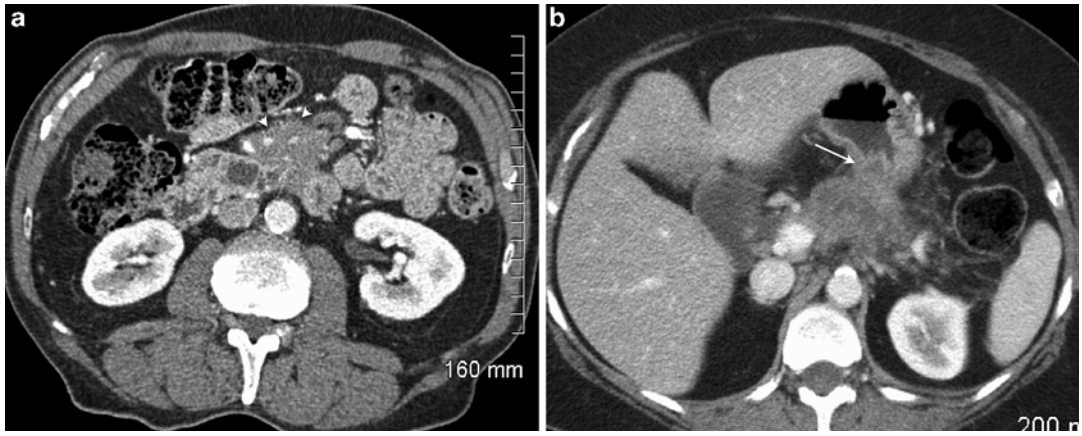

Fig. 2.10 Pancreatic adenocarcinoma with extension into the small bowel mesentery (**a**, *arrowheads*) and into the posterior gastric wall (**b**, *arrow*)

Magnetic Resonance Imaging

Although most centers use MDCT as the primary examination for staging pancreatic cancer, MRI is a useful alternate imaging modality for both detection and staging, particularly when contrast-enhanced MDCT is contraindicated [14]. MR is equivalent to MDCT for detection and assessment of local disease [24–26]. On T1 weighted images, the normal pancreas is relatively hyperintense due to the higher content of protein in the pancreatic acini [10]. This is more conspicuous on T1 weighted images with fat suppression (Fig. 2.13). Tumors are hypointense to isointense to the normal pancreas on T1 weighted images [27]. On T2 weighted images, tumors are usually hyperintense to isointense (Fig. 2.14) [27]. Heavily T2 weighted images acquired for MR cholangiopancreatography (MRCP) will demonstrate the level of biliary or pancreatic ductal obstruction if present (Fig. 2.15) [28]. The atrophic parenchyma in the region of upstream pancreatic ductal dilation may demonstrate decreased signal on the T1 weighted images [10]. With gadolinium-based intravenous contrast administration, images are acquired using fast T1 weighted fat-suppressed 3D gradient echo sequences, also allowing for multiphase acquisitions [29] similar to MDCT (Fig. 2.16). The enhancement characteristics of

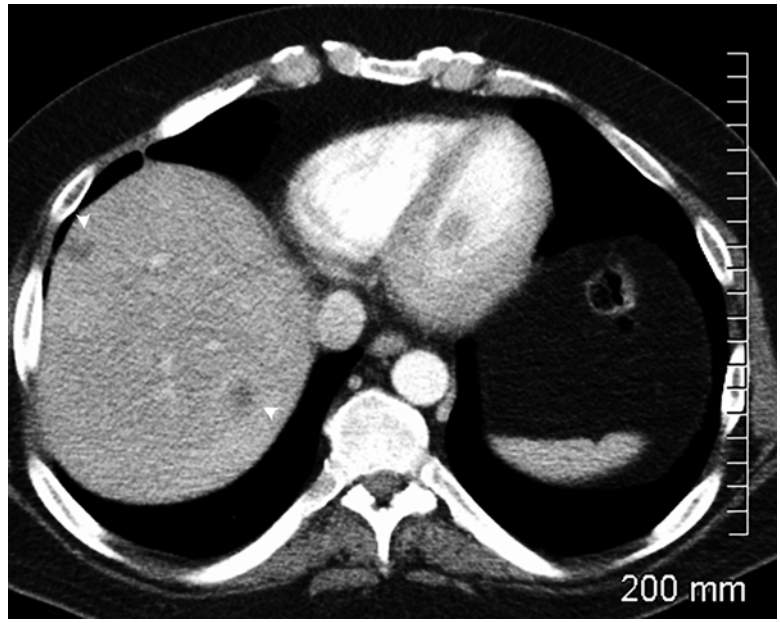

Fig. 2.11 Hypodense liver lesions (*arrowheads*) representing metastatic disease

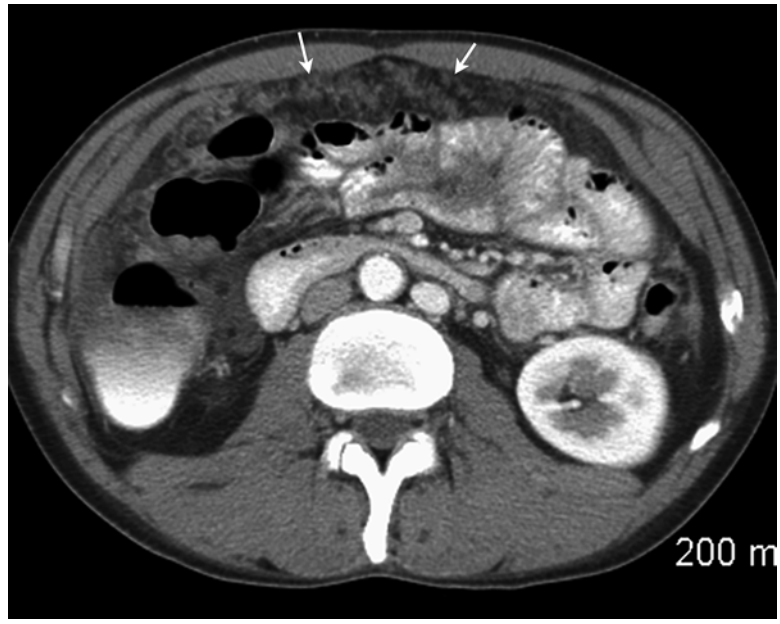

Fig. 2.12 Omental nodules (*arrows*) are consistent with peritoneal carcinomatosis. A small amount of free fluid is also present

normal pancreatic parenchyma and tumor are similar to CT, with pancreatic adenocarcinoma enhancing less than normal parenchyma in the arterial and portal venous phases. Lesion conspicuity is greatest on the arterial phase images (Fig. 2.17) [29]. On diffusion weighted images, pancreatic carcinoma tends to have restricted diffusion [10], but these images are less sensitive than the contrast-enhanced images for tumor detection [29]. In addition, diffusion weighted images are unable to differentiate between pancreatic adenocarcinoma and mass forming chronic pancreatitis [30, 31]. Assessment of vascular involvement may also be performed by MR with equivalent performance to MDCT for determination of resectability [32]. Preservation of the fat

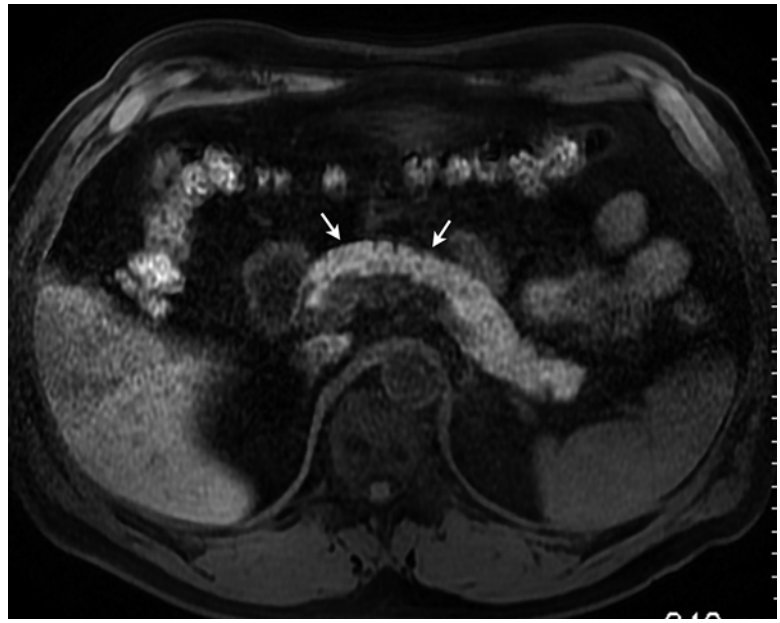

Fig. 2.13 Fat-suppressed T1 weighted spoiled gradient echo image demonstrates bright T1 signal intensity of the normal pancreas (*arrows*)

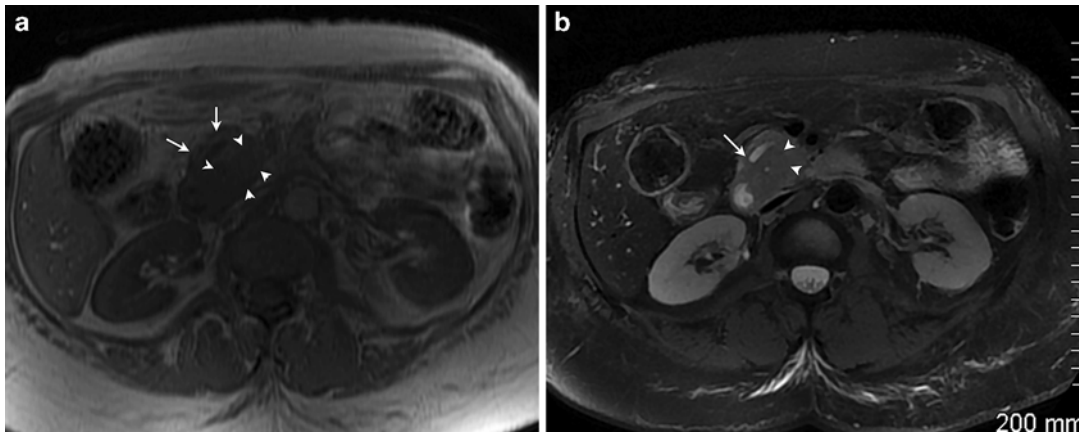

Fig. 2.14 Tumor (*arrowheads*) is hypointense to the pancreas (*arrow*) on the T1 weighted image. (**a**) On the fat-suppressed T2 weighted image (**b**), the mass (*arrowhead*) is isointense to slightly hypointense to the pancreas. A dilated pancreatic duct (*arrow*) is seen

plane between tumor and vessel is seen as a persistent high T1 signal fat surrounding the vessel on non-fat suppressed T1 weighted images.

MRI can be useful in detecting tumors that are isoattenuating on CT (Fig. 2.18) [27], with a reported sensitivity of 79.2 % of this group of tumors [17]. MRI may also have a benefit in the imaging of small tumors (less than 2 cm) [10].

Evaluation for metastatic disease is well documented by MRI. MR evaluation of the liver is better than MDCT at characterizing small lesions [10, 33] since cysts and hemangiomas are high signal on T2 weighted images and contrast enhancement patterns are characteristic (Fig. 2.19). MR evaluation with agents that are taken up by normal hepatocytes on delayed imaging (gadoxetic acid) is more sensitive for the detection of hepatic metastases but also allows for the detection of tumor and evaluation of local extent of disease [34].

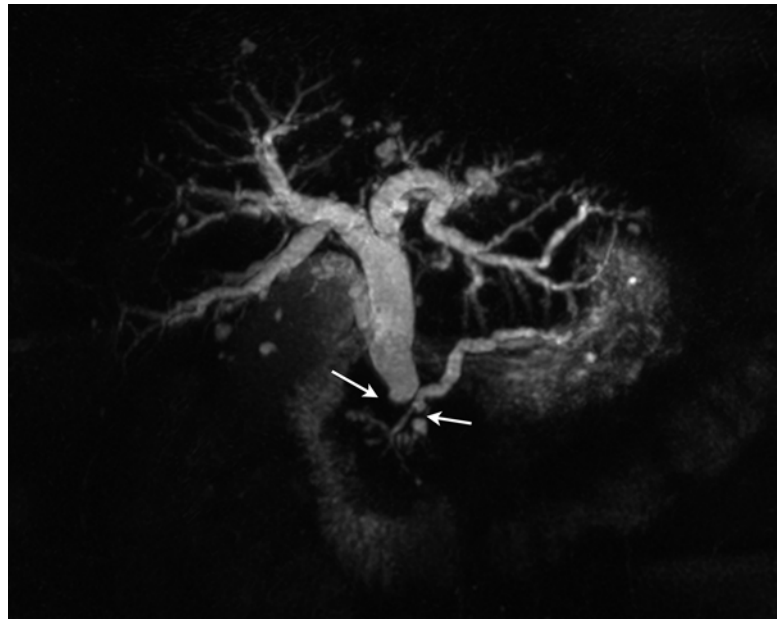

Fig. 2.15 3D MRCP image demonstrates the level of biliary and pancreatic ductal dilation (*arrows*)

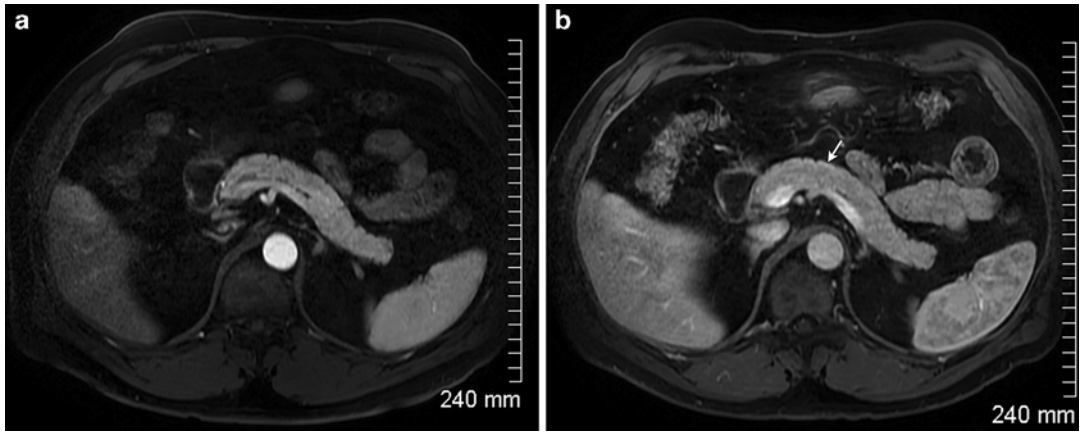

Fig. 2.16 Arterial phase (**a**) and portal venous phase (**b**) images of a normal pancreas with homogeneous enhancement

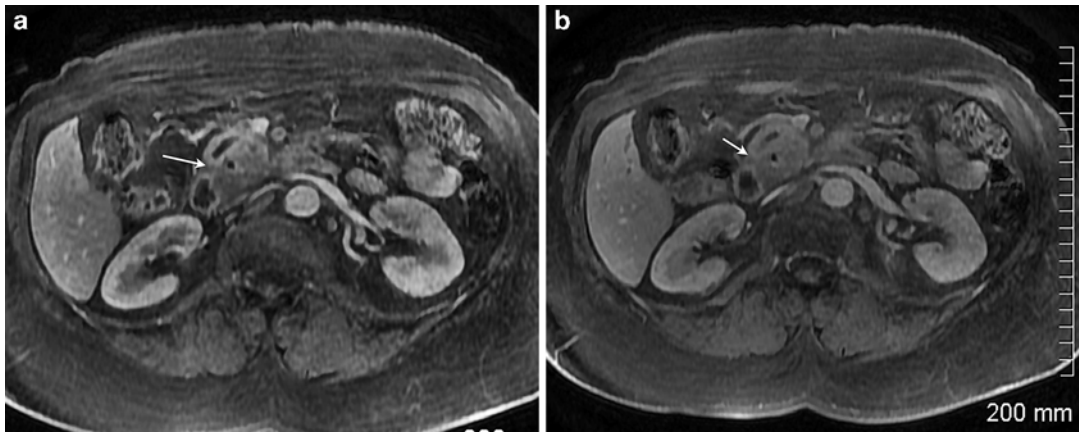

Fig. 2.17 Arterial phase (**a**) and portal venous phase (**b**) images demonstrate greater signal intensity difference between the tumor and the pancreas (*arrow*) on the arterial phase study (**a**)

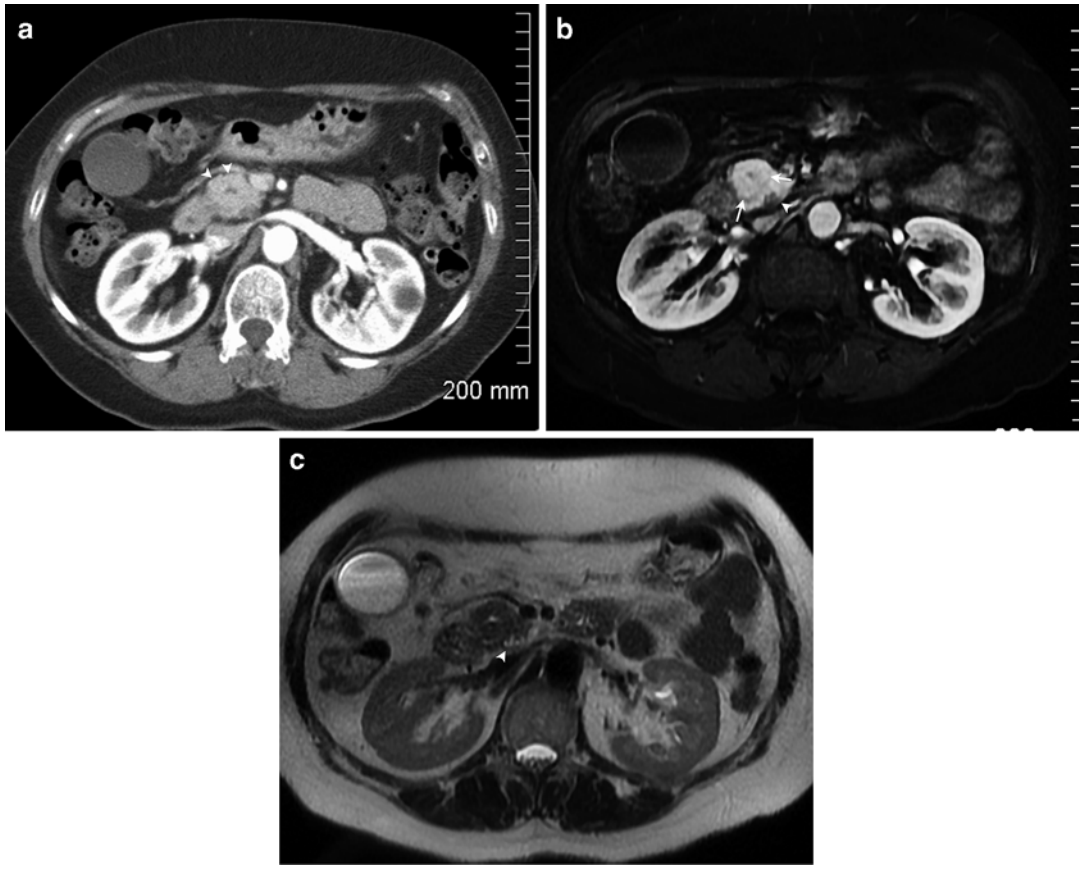

Fig. 2.18 In the same patient as seen in Fig. 2.3 (**a**), the tumor is now visible on the contrast-enhanced study (**b**, *arrows*). The small hypointense focus (*arrowhead*) seen posterior to the tumor is shown to represent a dilated pancreatic ductal sidebranch on the T2 weighted image (**c**)

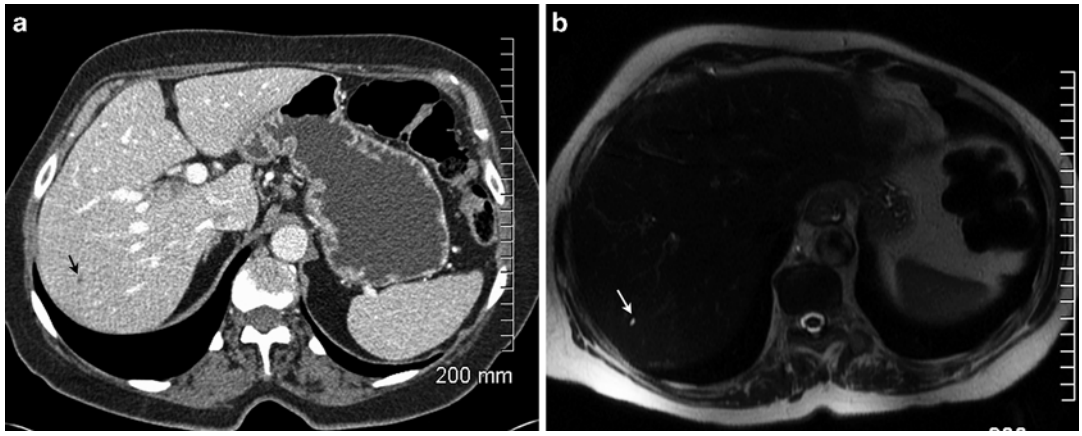

Fig. 2.19 A tiny low attenuation lesion (*arrow*) is seen on CT (**a**). On T2 weighted MR (**b**), the lesion is well circumscribed and high in signal intensity consistent with a cyst

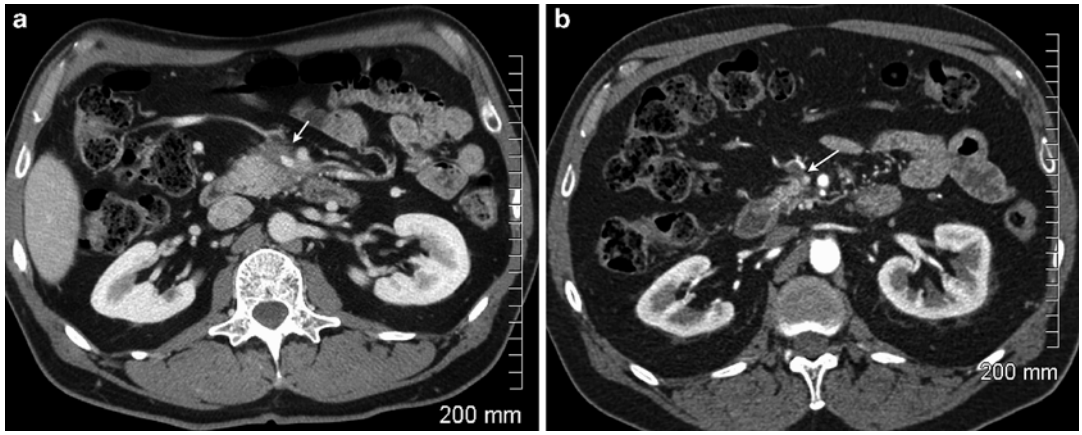

Fig. 2.20 Tumor (*arrow*) is seen deforming the superior mesenteric vein prior to therapy (**a**). Following neoadjuvant therapy (**b**), there is residual, but less extensive soft tissue (*arrow*)

Positron Emission Tomography/ Computed Tomography

At this time, ^{18}fluorodeoxyglucose (FDG) PET/CT has no role in the assessment of the local extent of pancreatic carcinoma [35]. The limited CT images are performed for attenuation correction and are routinely performed without intravenous contrast which is not adequate for evaluation for local vascular involvement [36]. ^{18}FDG uptake by the tumor limits also evaluation of the local tissues [10, 37]. The role of ^{18}FDG PET/CT in detection and evaluation of metastatic and recurrent disease is evolving [38, 39].

Imaging Following Therapy

Following neoadjuvant therapy for borderline resectable and unresectable locally advanced tumor, MDCT is less sensitive for prediction of potential resectability [40, 41]. This may be due to the inability to differentiate residual soft tissue at the tumor bed as either residual tumor or fibrosis (Fig. 2.20) [41]. Following therapy, the degree of vascular involvement may also be overestimated [40]. In a recent study, decreasing contact between tumor and the superior mesenteric vein or portal vein and decreasing contact with the superior mesenteric artery were associated with an R0 resection. However, decreasing tumor size was not significantly associated with an R0 resection [42].

Reporting

A multidisciplinary expert group sponsored by the Society of Abdominal Radiology and the American Pancreatic Association recently provided a consensus statement and reporting template for pancreatic ductal adenocarcinoma to facilitate complete reporting of the imaging findings [11, 43]. This document provides guidelines for comprehensive description of the primary tumor with characterization of the interface between tumor and adjacent vasculature and evaluation of extrapancreatic disease. Documentation of pertinent vascular variants is also included. Utilization of a structured reporting template is favored to provide consistent image interpretation and reproducible reports.

Summary

In summary, the clinical staging of pancreatic carcinoma is dependent upon optimal cross-sectional imaging, either MDCT or MRI. With both imaging modalities, multiphase imaging is needed to detect the tumor, to evaluate the relationship of the tumor to adjacent vasculature for potential

resectability, and to evaluate for metastatic disease. MDCT is more commonly used, but MRI is an alternative modality. MRI can be beneficial in detecting tumors that are isodense on CT and is better at characterizing small liver lesions.

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Endoscopic Ultrasonography: Staging and Therapeutic Interventions

3

Girish Mishra and Rishi Pawa

EUS: Staging and Operating Characteristics

Endosonography or Endoscopic Ultrasound (EUS) was initially developed approximately 25 years ago for the evaluation of gastrointestinal lesions and specifically, primary staging of GI malignancies. The relative merits of EUS for staging accuracy will be presented in greater detail in the ensuing paragraphs. The ability to determine resectability remains paramount for all imaging modalities. Large meta-analyses and comparative studies purport a degree of superiority for EUS in assessing the subset of patients deemed to be borderline resectable [1, 2]. Thorough review may point to a more neutral or equivocal view regarding such claims. In theory, however, EUS is well suited for providing the detail necessary to determine borderline resectable pancreatic cancer.

The advent of the mechanical scanning radial echoendoscopes allowed for elegant images in a 360° imaging plane very similar to computed tomography (Fig. 3.1). However, widespread acceptance of EUS has largely been due to the emergence of the linear array echoendoscope. The rapid refinement of the linear echoendoscope, both in scope design and imaging resolution coupled with an improvement in the accessory channel has allowed for constantly evolving therapeutic options including fine-needle aspiration (FNA) [3, 4]. Compared to conventional ultrasound, EUS is literally positioned within a few millimeters from the area of interest, such as the pancreas, making this an ideal diagnostic and therapeutic tool for pancreatic carcinoma. "Dead space" can be circumvented so that the ultrasound waves are targeted directly to the pancreatic parenchyma. Furthermore, EUS utilizes high-frequency probes that range from 5 to 20 MHz at the tip of the endoscope. This increased frequency when combined with the decreased distance needed for the ultrasound wave to travel, allow for the high-resolution images of the main pancreatic duct and surrounding parenchyma such that structures as small as 2–3 mm can be distinguished [5].

Perhaps in no other disease state has the widespread use of the linear echoendoscope become more apparent than in pancreatic cancer. In addition to vascular staging, the immediate advantage of tissue confirmation is implicit. Initial primary staging, followed by FNA of either the pancreatic mass itself or of lymph

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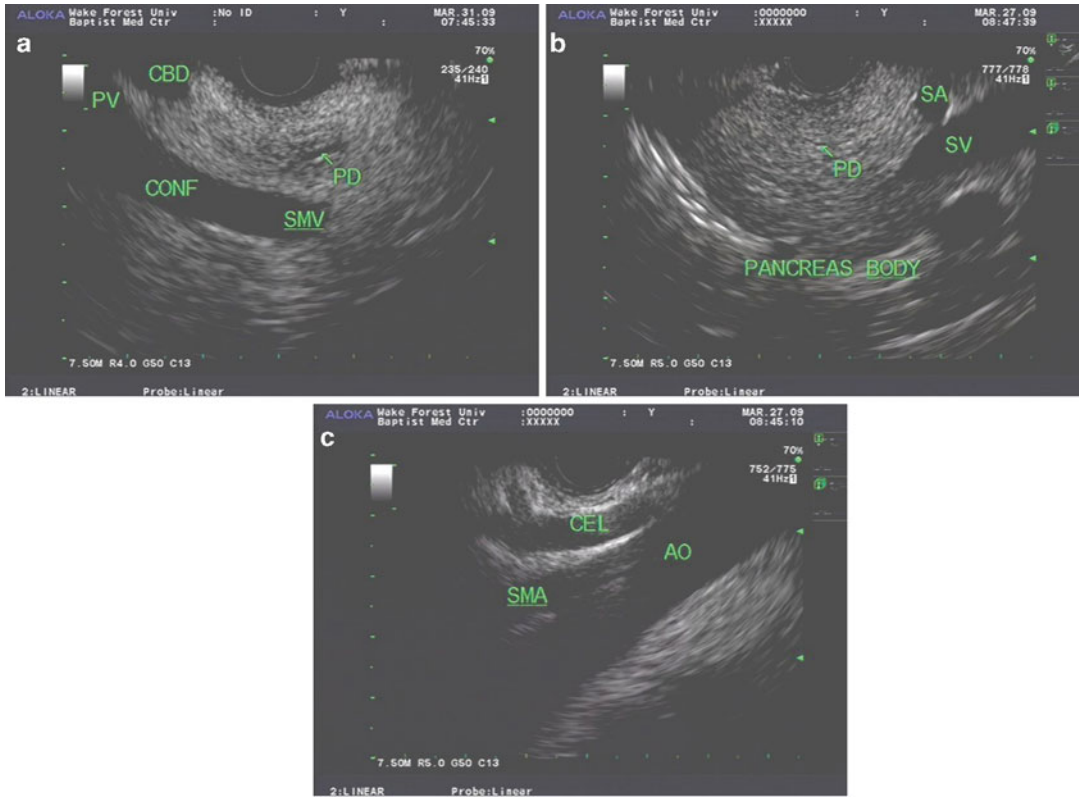

Fig. 3.1 Normal anatomy of the pancreas using a linear echoendoscope (**a**) head of the pancreas with the SMV/PV confluence. (**b**) Body of the pancreas with the main pancreatic duct (**c**) imaging of the celiac trunk and celiac artery take-off

nodes, to the ultimate ability to deem the patient as having unfortunate distant metastasis to organs such as the liver via tissue confirmation at the same setting make the linear echoendoscope the preferred instrument. Using a "station approach," one can obtain excellent views of the uncinate pancreas (with the EUS scope tip near the ampulla), head of the pancreas (with the EUS scope tip in the duodenal bulb), body of the pancreas (with the EUS scope tip in distal stomach), and tail of the pancreas (with the EUS scope tip in the gastric fundus). The left lobe of the liver is best seen with the scope along the lesser curve of the stomach and the scope tip at the body/antrum junction. Metastatic lesions to the left lobe can be easily seen, especially those abutting the gastric wall and amenable to FNA (Fig. 3.2). The working channel (which varies in diameter from 2 to 3.8 mm) is designed so that as the FNA needle is advanced, it will be within the plane of scanning and can be visualized as it enters the target tissue.

Radial Versus Linear Echoendoscope

Several studies emerged in the late 1990s that specifically compared radial scanning with the linear array for primary staging of pancreatic cancer as well as the utility of the linear array scope in both benign and malignant pancreatic lesions. The first study performed by Gress et al. utilized a cohort of 79 patients referred with pancreatic cancer [6]. As only 33 patients ultimately had surgical excision, the evaluable groups consisted of 17 patients randomized to linear array

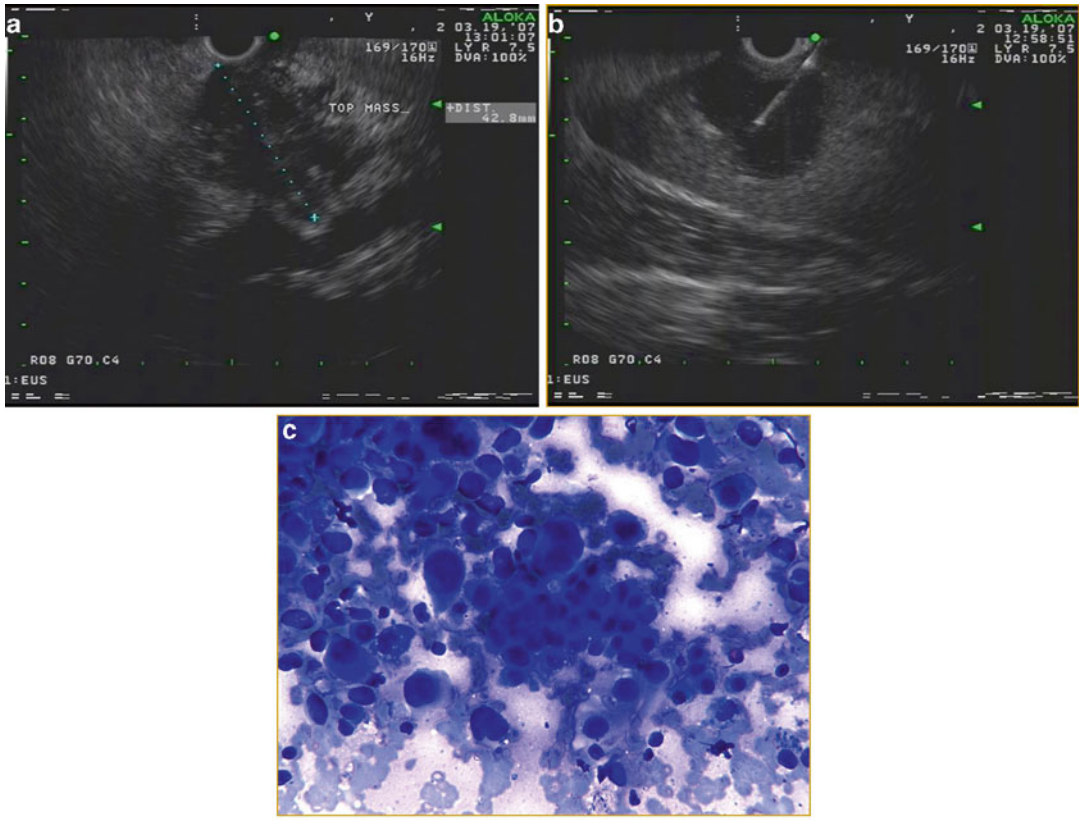

Fig. 3.2 (**a**) EUS image of an approximately 4.2 cm mass in the tail of the pancreas with irregular borders (**b**) FNA using a 25-gauge needle of a large metastatic lesion in the left lobe of the liver (**c**) cytology from the liver showing large, irregular cells consistent with metastatic adenocarcinoma

and 16 to radial scanning EUS. EUS staging accuracy for linear array was 94 % (16 of 17) for T and 71 % (12 of 17) for N staging. The staging accuracy for radial scanning was 88 % (14 of 16) for T and 75 % (12 of 16) for N staging. Surprisingly, radial scanning was more accurate for predicting vascular invasion 100 % (16 of 16) than the linear array 94 % (16 of 17). More recent literature militates against EUS superiority in assessing for vascular invasion. Seicean et al. explored the staging accuracy of radial EUS in pancreatic cancer and how well EUS can predict tumor resectability in 30 patients with pancreatic masses staged by both a radial EUS and surgery [7]. Resectability was based on EUS involvement of either the celiac trunk or superior mesenteric artery. Specific EUS criteria for vascular invasion were defined as direct visualization of loss of hyperechoic vascular wall, tumor ingrowth with complete vascular obstruction or the presence of peripancreatic venous collaterals. The accuracy of EUS T staging was 86.6 %, N staging was 93.3 %, while that of vascular invasion was 80 %. These authors advised using adjunct imaging modalities to a radial EUS for assessing arterial invasion. Conventional radial and linear echoendoscopes offer 2D imaging. However, 3D imaging would be ideal when assessing for vascular invasion. Fritscher-Ravens et al. describe their experience using a linear echoendoscope to identify a pancreatic tumor followed by 3D image acquisition using a magnetic tracked 3D sensor [8]. The EUS results from 22 patients with solid pancreatic lesions (17 adenocarcinomas, 5 chronic pancreatitis) were compared to surgical histology. In 30 % of cases, the 3D reconstruction

suggested vascular compression rather than vascular invasion. One patient was incorrectly classified as having vascular invasion with the 3D reconstruction. Although 3D reconstruction is largely investigational, this study is tantalizing for the prospect of achieving greater clarity of vascular involvement by EUS preoperatively.

EUS Versus Other Imaging Modalities

The initial excitement of the superior imaging qualities provided by EUS for pancreatic cancer has now been tempered by the reality that newer generation computed tomography (CT) scanners with 3D reconstruction allow for superb imaging and, thus, staging. Nonetheless, reviewing the literature offers insights as to the relative merits for each technology. A landmark study by DeWitt and colleagues compared EUS and multidetector CT for the detection, staging, and resectability of known or suspected locoregional pancreatic cancer using a prospective, observational cohort [9]. EUS followed by multidetector CT was performed in 104 patients; patients with known or suspected pancreatic cancer felt to be resectable by 1 or both tests were considered for surgery. Of the 80 patients with pancreatic cancer, 27 (34 %) were managed nonoperatively and 53 (66 %) underwent surgery ($n=25$, resectable; $n=28$, unresectable). The sensitivity of EUS for detecting a pancreatic mass was 98 % [95 % CI, 91–100 %]; the sensitivity for CT was 86 % [CI, 77–93 %]; $p=0.012$. EUS was superior to CT for tumor staging accuracy (67 % vs. 41 %; $p<0.001$) but equivalent for nodal staging accuracy (94 % vs. 47 %; $p>0.2$). In the 25 patients recommended for surgery, EUS correctly identified 88 % of patients whereas CT correctly identified 92 % of patients. In the 28 unresectable pancreatic tumors in the patients recommended for surgery, EUS and CT correctly identified 68 % and 64 %, respectively. The investigators teased out characteristics of masses undetected by EUS ($n=2$) and CT ($n=10$) in patients undergoing surgery. Nine of these missed lesions by CT were ≤25 mm. The authors' conclusions echoed most diagnosticians in the field that a preoperative EUS should be performed when a CT fails to detect a mass in patients with suspected pancreatic cancer (Fig. 3.3).

As mentioned above, EUS allows for detailed imaging to assess for vascular involvement prior to planned surgery. However, recent studies question the ability of expert endosonographers to accurately assess for vascular involvement [10, 11]. Rösch and colleagues showed videotapes of 75 patients with cancer involving the pancreatic head and asked to assess for involvement of either the portal vein confluence, superior mesenteric vein, or the celiac axis. The investigators withheld clinical information from the EUS experts to exclude potential bias. The sensitivity and

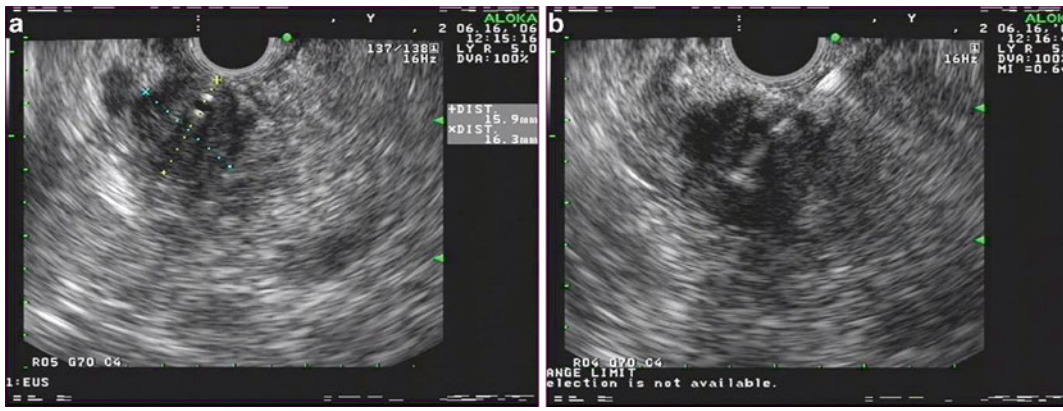

Fig. 3.3 (**a**) Linear EUS image of an approximately 1.6 × 1.6 cm mass in the pancreatic head with a biliary stent. This lesion was not detected by CT (**b**) FNA of pancreatic head mass, positive for adenocarcinoma

specificity of EUS in the diagnosis of venous invasion were 43 % and 91 %, respectively, when using parameters such as visualization of tumor in the lumen, complete obstruction, or collateral vessels. The portal vein confluence was the only vascular system that could be properly visualized. A more recent study from Aslanian and colleagues compared EUS with surgical findings of vascular adherence and the pathology finding of vascular invasion among patients undergoing resection of pancreatic masses [12]. Vascular adherence was defined as tumor adherence requiring vascular resection and vascular invasion was defined as histologic invasion of vessel wall by tumor. They used both the radial and linear echoendoscopes. Thirty of 68 patients were eventually resectable. Sensitivity, specificity, PPV, and NPV of EUS were 63 %, 64 %, 43 %, and 80 % for vascular adherence and 50 %, 58 %, 28 %, and 82 % for vascular invasion, respectively. Similar to Rösch's study, Aslanian and colleagues found that the NPV rose to 90 % for vascular adherence if only the portal confluence was considered.

An in-depth evaluation of the ability of EUS and CT to predict an R0 resection is absolutely germane as we constantly strive to offer our patients the greatest opportunity for cure and long-term survival when dealing with pancreatic cancer. Data derived from both CT and EUS are often necessary to determine the best treatment options, often with a multidisciplinary approach. The complementary roles for both EUS and CT are best highlighted by a recent study specifically investigating the ability of EUS and CT to predict a margin-negative R0 resection in patients undergoing a pancreaticoduodenectomy [13]. A linear echoendoscope was used in 76 patients. The endosonographers were blinded to prior imaging results and clinical outcome and reviewed either a video or the procedure note with pictures and noted the involvement of the superior mesenteric vein and artery, celiac axis, hepatic artery, portal vein, lymph nodes, and liver. Their definitions were similar to those used by prior investigators and included vessel abutment (loss of the hyperechoic interface between the tumor and vessel), vessel invasion (visualization of tumor within the lumen), vessel encasement, and vessel occlusion (Fig. 3.4). Using a subgroup of 27 evaluable patients who did not have a biliary stent, and using the above criteria, when EUS detected either venous invasion or abutment, there was an association with incomplete resection giving a sensitivity, specificity, PPV, NPV, and accuracy of 79 %, 69 %, 73 %, 75 %, and 74 %, respectively. In line with other studies, Bao and colleagues noted that EUS findings of arterial involvement were inaccurate, with three of six patients achieving an R0 margin despite the EUS report.

Clinically, it is not uncommon to attempt EUS staging after the placement of a transpapillary biliary stent by endoscopic retrograde cholangiopancreatography (ERCP) for malignant biliary obstruction. However, biliary stents can cause acoustic reverberation and shadowing, artifacts that can distort the outer margins of a mass, hampering the excellent views critical for EUS staging. This technical impediment was supported by a few studies that cautioned against the high accuracy rates for EUS staging [14, 15]. In fact, Kim et al. found that patients with biliary stents had lower accuracy of EUS-FNA for malignancy (77 %) than those without a biliary stent (89 %). These reports subsequently led to studies to specifically address the potential negative impact of a biliary stent (both plastic and metal) on staging accuracy and diagnostic yield for FNA [16–19]. These studies are limited due to retrospective study designs. However, the findings from these studies uniformly and consistently conclude that neither a metal nor a plastic biliary stent hampers accurate EUS staging or the high yield of EUS-FNA.

So, how does EUS compare to CT and other imaging modalities for staging of pancreatic cancer after factoring in the relative strengths and weaknesses of both modalities? Advances in cross-sectional imaging allow detailed views of the pancreas and the surrounding vasculature to warrant its use as a first-line modality for detection and staging when pancreatic cancer is suspected [20, 21]. Meta-analyses comparing these

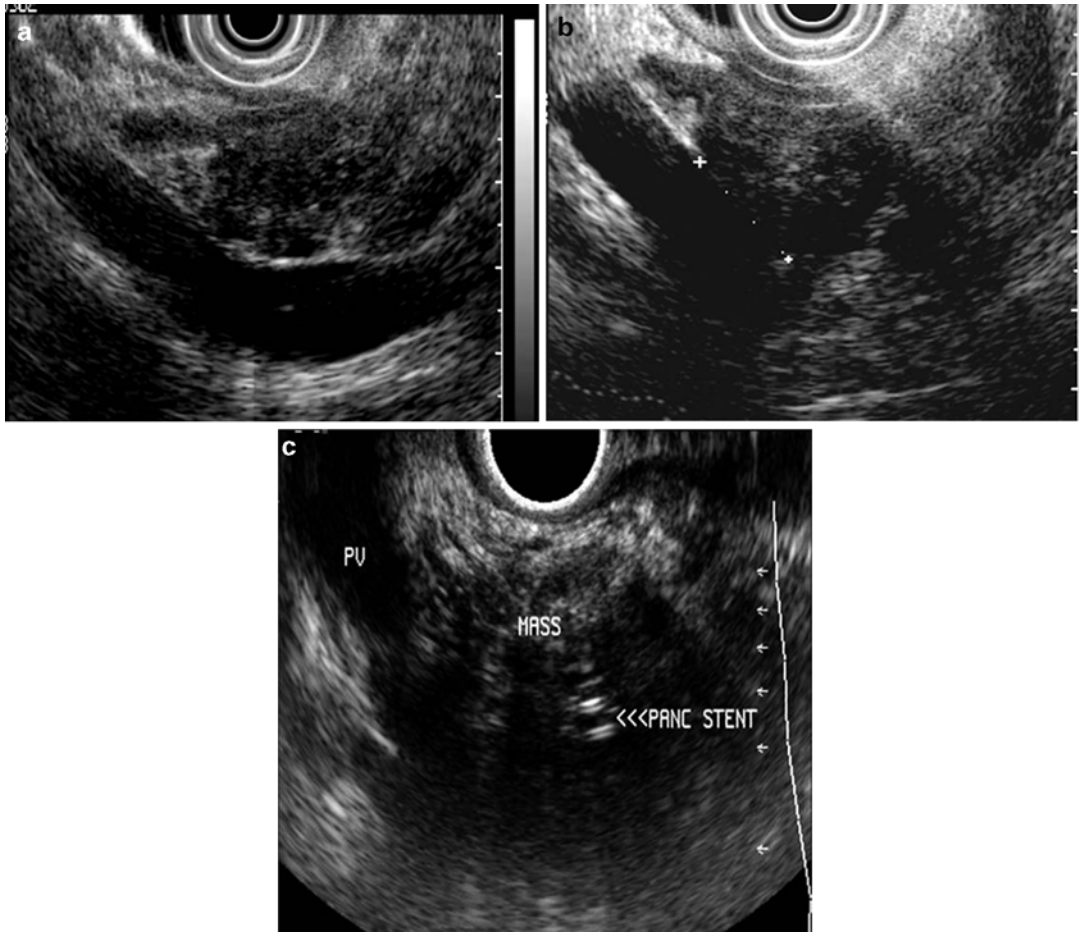

Fig. 3.4 EUS interpretation of vascular invasion (**a**) resectable pancreatic head mass with abutment (**b**) resectable pancreatic head mass with a short segment of adherence to the portal vein (**c**) unresectable pancreatic head mass due to portal vein invasion. A pancreatic stent is noted within the mass. (Images courtesy of Dr. Shyam Varadarajulu)

two technologies highlight the methodological limitations, heterogeneity in study design, quality, and results [22–24]. Interpretation of the results is further marred by the lack of technical uniformity in the CT scans and echoendoscopes used in the differing studies. These studies do, however, favor a slightly increased sensitivity for EUS in detecting pancreatic lesions less than 3.0 cm. If pancreatic cancer is detected with evidence of distant metastases, then there is no role for EUS outside of a research protocol or need for tissue acquisition prior to planned therapy. If however, the CT does not show a mass and the clinical suspicion for pancreatic cancer is high, then an EUS should be performed at which time an FNA can also be performed [25, 26].

Finally, and of great consolation for our patients and healthcare providers is the finding of a normal EUS when searching for a pancreatic cancer. EUS is associated with the best negative predictive value in patients with suspected pancreatic cancer [27–30]. Klapman and colleagues retrospectively reviewed nearly 700 patients with suspected pancreatic cancer who underwent EUS over a 4-year period. The NPV of EUS in excluding pancreatic cancer was 100 % over a mean

follow-up of 25 months (range 8–48 months). In addition, 88 % of patients required no further work-up following the EUS.

Adjunct EUS Methods to Improve Detection

Contrast Enhancement

Contrast enhanced (CE) images are routinely used to better visualize mass lesions as well as the vasculature during cross-sectional imaging. Typically, malignant pancreatic masses present as hypoechoic lesions on EUS. However, benign pancreatic masses (either inflammatory or autoimmune) can often be difficult to distinguish on imaging, thus, necessitating an FNA. Intravenous US agents consist of microbubbles filled with heavy gases that allow for better visualization of the blood supply [31]. Contrast enhanced EUS (CE-EUS) allows for noninvasive visualization of the blood flow in small vessels as well as the microvasculature surrounding the target lesion of interest using harmonic imaging (CEH-EUS) [32]. Many of the commercially available agents used for enhancement in conventional ultrasonography cannot be used with EUS—the smaller transducer size and acoustic power of EUS limits use of certain agents. In a pilot study with 35 patients, Napolean and colleagues used an intravenous injection of a second-generation ultrasound contrast agent SonoVue®, (Bracco, Milan, Italy) along with a new Olympus prototype echoendoscope capable of detecting extended harmonics (XGF-UCT 180, Olympus America, Melville, NY) [33]. Sixteen of the 18 adenocarcinomas gave a hypointense signal on CEH. The sensitivity, specificity, NPV, PPV, and accuracy of hypointensity for diagnosing pancreatic adenocarcinoma were 89, 88, 88, and 89 %, compared with 72, 100, 77, 100, and 86 % for EUS-FNA. Several other studies have shown similar results—a hypoechoic mass on CEH-EUS was highly sensitive for pancreatic adenocarcinoma [34, 35]. In fact, Fusaroli et al. found that hyperenhancement specifically excluded adenocarcinoma (98 %).

Sonoelastography

The advent of newer needle designs when combined with greater experience by endosonographers and cytopathologist have led to phenomenal yield by EUS-FNA for diagnosing pancreatic cancer. However, false-negative results between 20 and 40 % have been reported in technically challenging cases or in the setting of inflammatory masses such as chronic pancreatitis [36–38]. The ability to obtain "virtual biopsies" without FNA in order to distinguish benign from malignant solid pancreatic masses would fill the void of false-negative samples [39]. Elastography represents a novel addition to EUS in an ongoing quest to improve imaging and help differentiate benign from malignant pancreatic masses technology that has evolved over the past 5 years. This technology can be applied with real-time ultrasound and relies on the firmness or elasticity of a given tissue relative to the adjacent normal tissue by measuring the strain or displacement generated in response to compression or vibration [40]. Conventional linear-array echoendoscopes (Pentax Medical, Montvale, NJ), an ultrasound platform (Hitachi 7500 or 8500, Hitachi) with an integrated elastography module can be used such that inflammatory masses or tumors will appear hard [41]. The elastography image can be superimposed over the conventional B-mode imaging such that hard tissue is depicted as blue, soft tissue in red, and tissue of intermediate elasticity as green-yellow (Fig. 3.5). This is termed qualitative elastography. Second-generation elastography or quantitative elastography attempts to remove the subjectivity by utilizing the ratio of the elasticity of a given mass to that of a selected region within adjacent soft tissue, termed the strain ratio (SR) [40]. Iglesias-Garcia et al. reported a 100 % sensitivity for both qualitative and quantitative elastography in 86 consecutive patients who underwent an EUS for the evaluation of solid pancreatic masses for distinguishing malignancy [42]. They reported an overall accuracy of 90.7 % using qualitative elastography and 97.7 % using strain ratio. Subsequent studies have not been

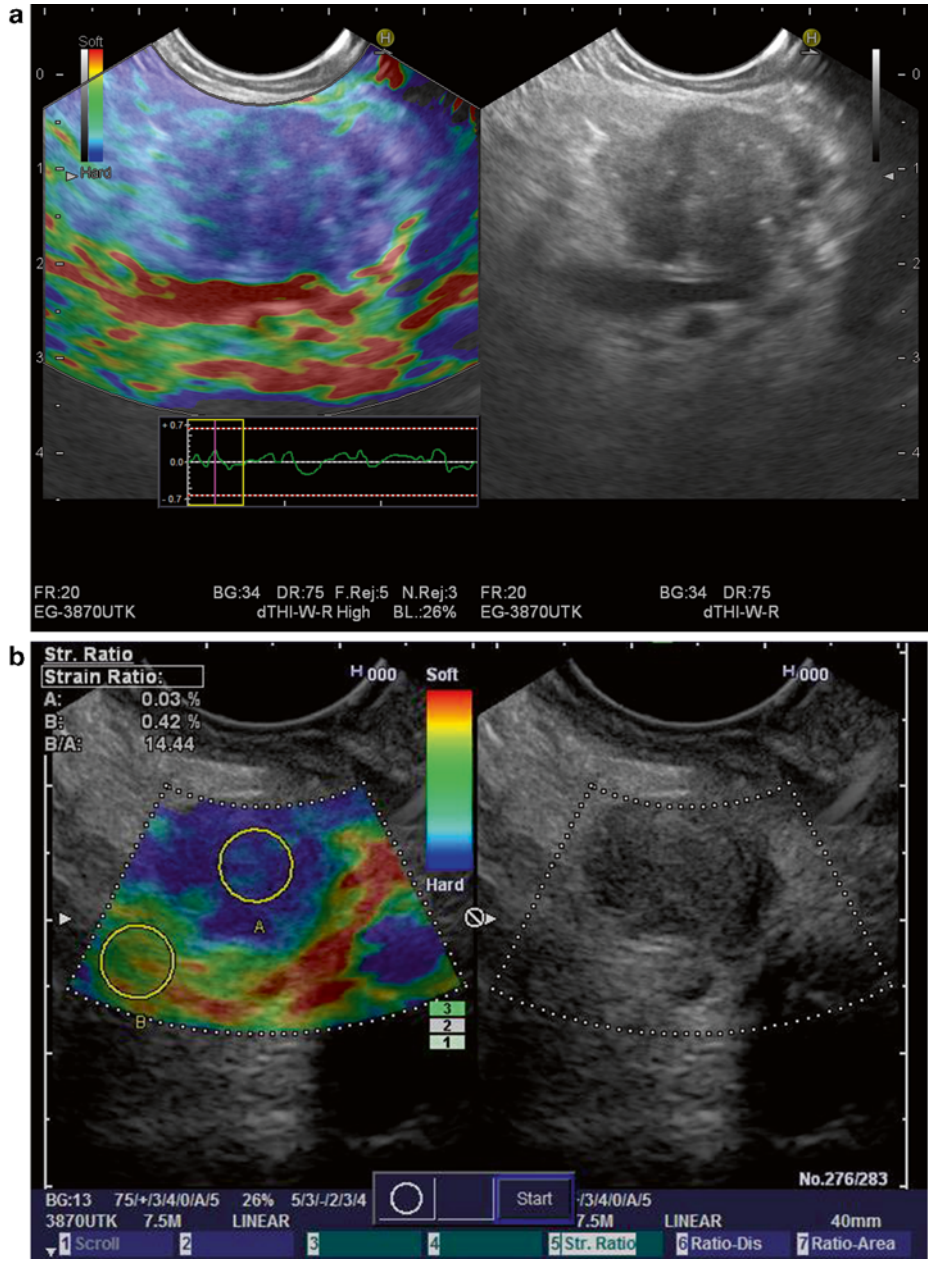

Fig. 3.5 (**a**) Sonoelastography images of a malignant pancreatic mass (**b**) sonoelastography images of malignant pancreatic mass with strain ratios (Images courtesy of Pentax Medical)

able to replicate the same impressive performance characteristics suggesting that at present, elastography cannot replace pancreatic tissue sampling [40]. Meta-analyses of EUS elastography underscore the somewhat contradictory findings using this technology [43, 44].

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) allows real-time imaging of the GI tract at approximately 1000-fold magnification such that the endoscopic images

resemble light microscopy with resolution of approximately 1 μm [45]. Tissue illumination via a laser and subsequent detection of the fluorescence of light reflected through the pinhole increases the spatial resolution of CLE allowing for in vivo real-time histopathology of the mucosal layer [46]. The two clinically available systems are either endoscopic (eCLE) manufactured by Pentax (Pentax America, Montvale, NJ) or through-the-scope probe (pCLE) (Cellvizio, Mauna Kea Technologies, Paris, France). eCLE has been used to detect dysplasia and neoplasia in Barrett's esophagus, classification of polyps, and assessment of resection margins after polypectomy, and evaluation of inflammatory disease [45, 47–51]. pCLE can be used for the above conditions but has steadily gained more acceptance for pancreatobiliary applications [52]. The diameter of the fiber can be as small as 300 μm. Such a small diameter fiber can be used to image the pancreatic duct, bile duct, and be inserted through the fine-needle system currently used for performing EUS-guided FNA (nCLE). An ERCP is often performed to evaluate biliary and pancreatic strictures. Using a CholangioFlex confocal probe with Cellvizio (Mauna Kea Technologies, Paris, France), either the bile duct or the pancreatic duct can be further accessed. Early reports from several small series suggest excellent agreement between cytology/histopathology and focal endomicroscopy [53, 54]. Kahaleh and colleagues reported a Kappa coefficient of agreement of 0.8 between cyto/histopathology and pCLE in 15/16 cases ($p=0.0001$). Furthermore, the clinical impact of the pCLE was such that 4 patients underwent a Whipple rather than a total pancreatectomy. Giovannini and colleagues found specific and reproducible patterns that reliably distinguished malignant from benign strictures using intraductal confocal microscopy (IDCM; Fig. 3.6). The presence of irregular vessels, large black bands, and black clumps seen on IDCM predicted neoplasia with a sensitivity of 83 %, specificity of 75 %, and accuracy of 86 % in 33 patients.

Further advancement and refinement using pCLE technology has led to the development of a prototype new confocal miniprobe that is flexible and small enough to be introduced through either a standard 19-gauge or 22-gauge puncture needle currently used for EUS-FNA (nCLE) (Mauna Kea Technologies, Paris, France). Becker and colleagues showed that it was technically feasible to obtain in vivo histology in a porcine model using nCLE through a 22-gauge needle (Fig. 3.7) [55]. Konda et al. have taken this concept, model, and needle design to evaluate pancreatic lesions in humans [56, 57]. They found that an nCLE was technically feasible in 17 of 18 cases (2 solid lesions) using a 19-gauge needle with moderate to good imaging qualities (1-pancreatic endocrine tumor; 1-adenocarcinoma) [56]. Two patients suffered mild pancreatitis in cystic lesions, perhaps due to the larger needle size used. Konda et al. performed a subsequent, pilot in vivo nCLE multicenter study in the Pancreas with Endosonography of Cystic Tumors (INSPECT) [57]. They found that the presence of epithelial villous structures based on nCLE was associated with pancreatic cystic neoplasms ($p=0.004$) and with a sensitivity of 59 %, specificity of 100 %, PPV of 100 %, and NPV of 50 %. The overall complication rate was 9 % with three cases of intracystic bleeding.

EUS-Guided Cholangiography Biliary Drainage

ERCP remains the procedure of choice for palliation of malignant biliary obstruction. Although technical success for ERCP hovers near 95 %, some caveats and challenges exist. Biliary drainage can elude even the most skilled biliary endoscopists in patients with variant anatomy, ampullary pathology, and/or malignant luminal obstruction. Traditionally, the drainage options when the papilla is not accessible include either percutaneous or surgical drainage [58–60]. The morbidity associated with these non-endoscopic approaches is high, especially in patients with advanced malignancy. EUS-guided biliary drainage (EGBD) provides an alternative for accessing the bile duct when transpapillary biliary cannulation fails (Fig. 3.8.) [61–64]. What makes it particularly attractive is that it can be performed in the same session as the originally failed ERCP without further delay. In addition, it provides immediate internal biliary drainage without the need for external drains. The first description of diagnostic

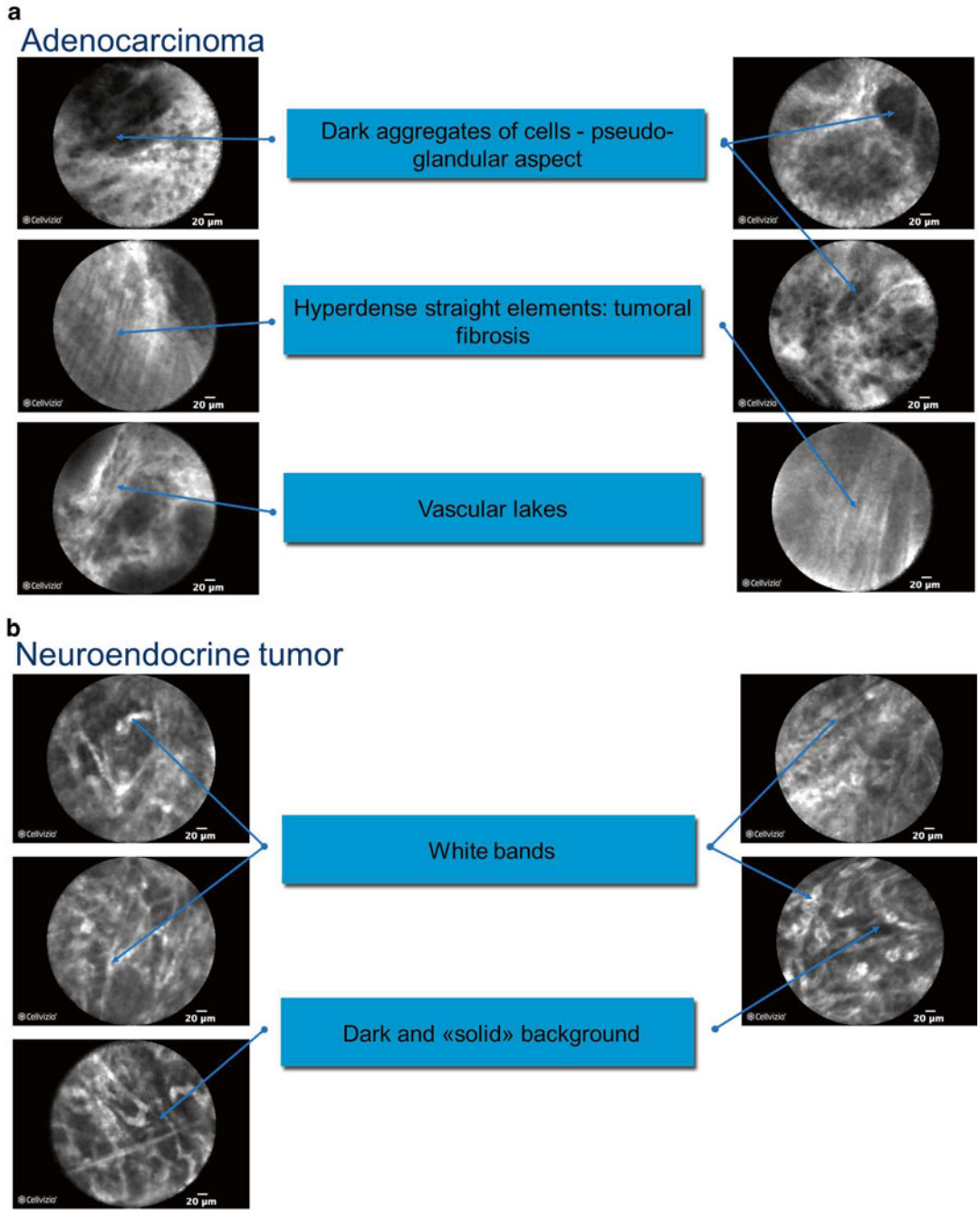

Fig. 3.6 (**a**) confocal laser endomicroscopy of pancreatic adenocarcinoma and (**b**) pancreatic neuroendocrine tumor (Images courtesy of Dr. Mark Giovannini)

tive trials, EGBD appears to allow an alternative technical approach for relieving biliary obstruction in select centers and with great caution.

EUS-Guided Fiducial Placement

In recent years, the development of image-guided radiation technique (IGRT) has allowed the delivery of precisely aimed radiation beams

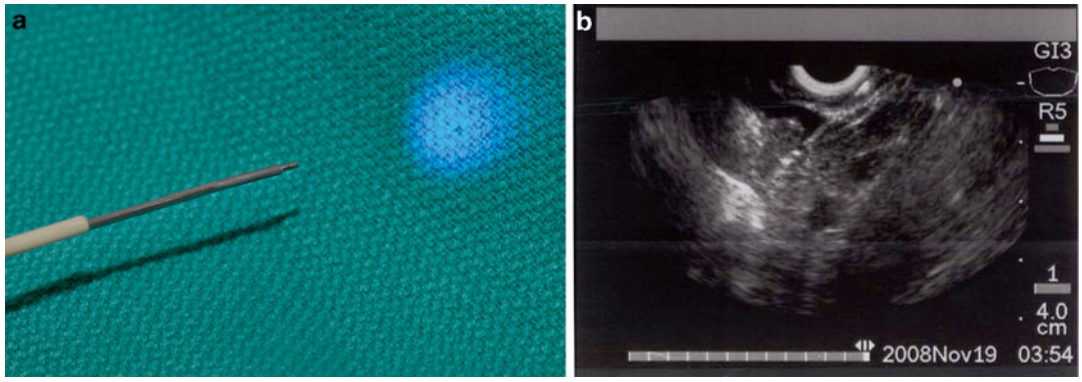

Fig. 3.7 (**a**) confocal probe through an EUS-FNA needle (nCLE) and (**b**) EUS image nCLE in a pig liver (Images courtesy of Dr. Michael Wallace)

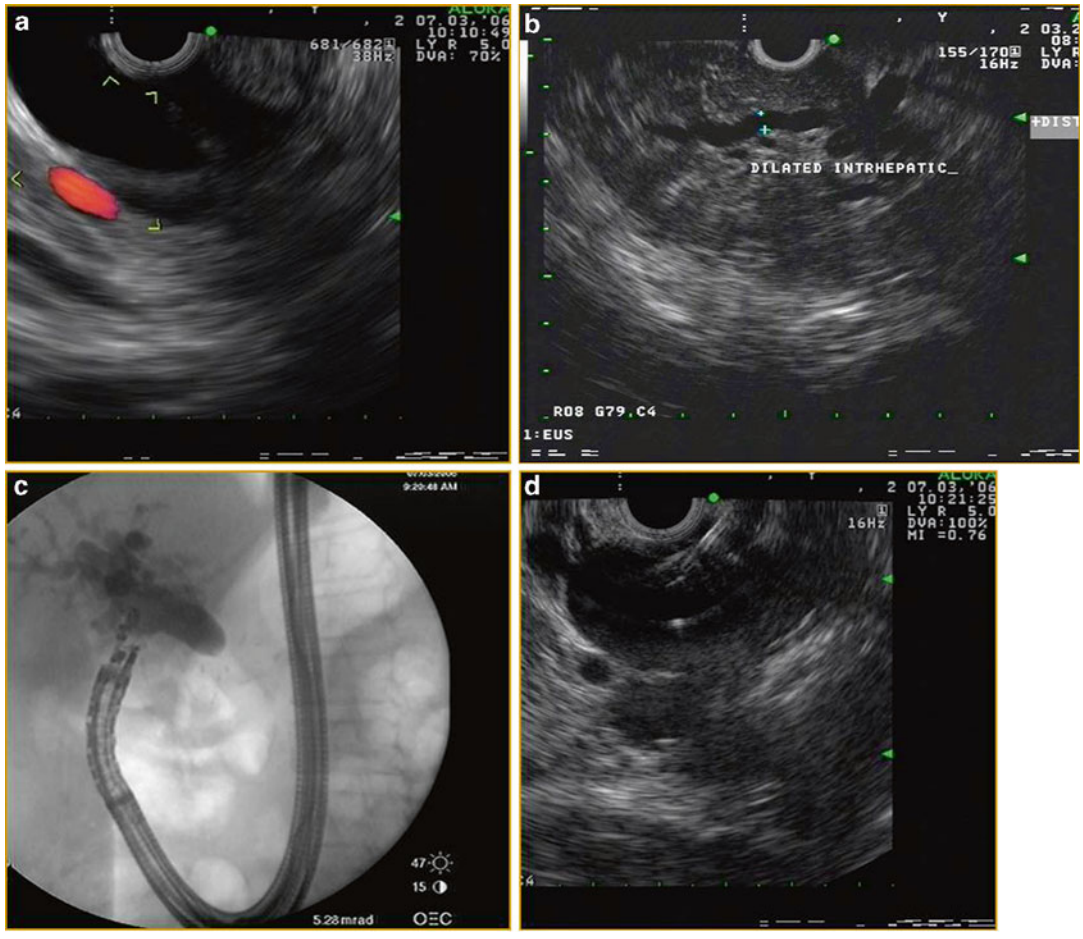

Fig. 3.8 Linear EUS images demonstrating EUS-guided cholangiography and biliary drainage after unsuccessful ERCP (**a**) EUS image of an approximately 2.0 cm, dilated CBD (**b**) EUS image of dilated intrahepatic ducts (**c**) fluoroscopic image of EUS-guided puncture of CBD and contrast injection (**d**) Puncture of CBD with a 19-g EUS needle (**e**) fluoroscopic image of guidewire placement via a 19-g EUS needle and antegrade passage of wire through the (**f**) papilla (**g**) deployment of metal biliary stent

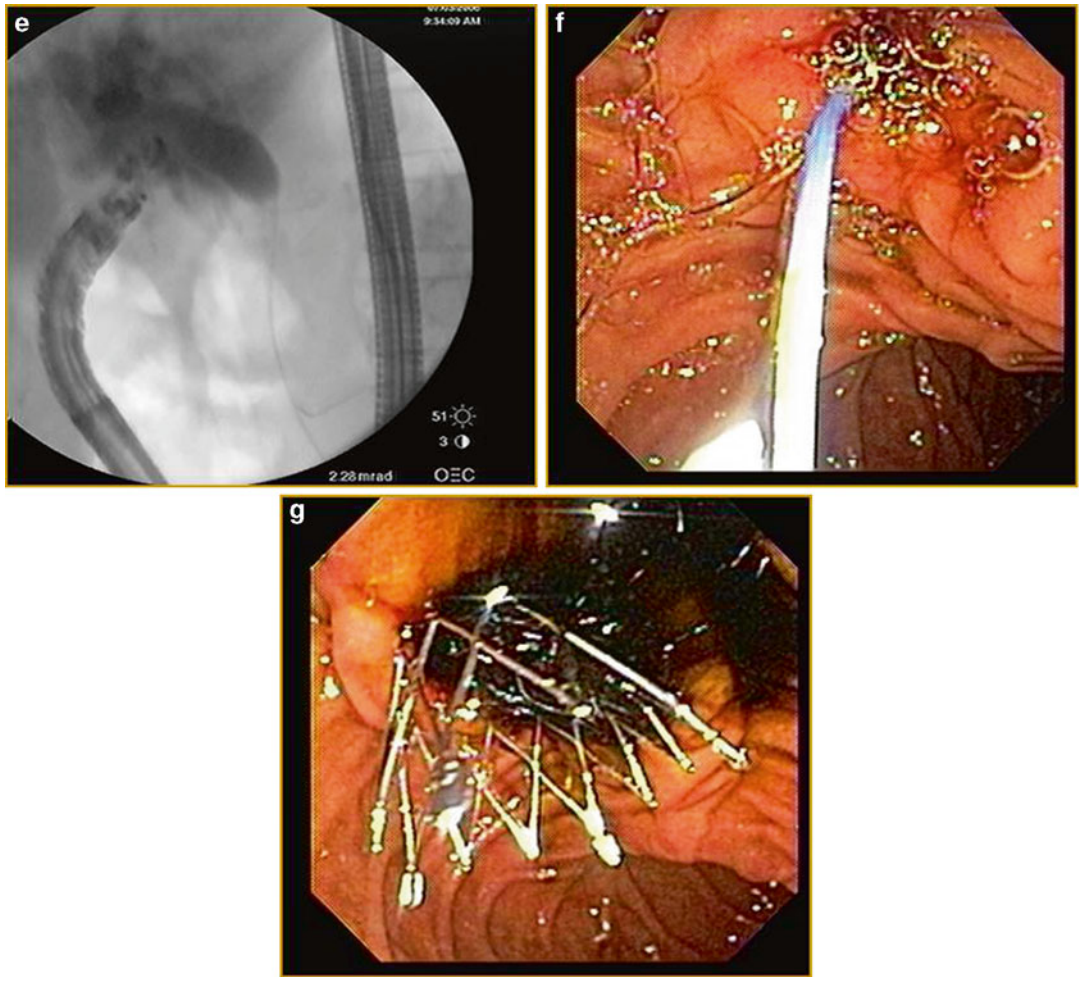

Fig. 3.8 (continued)

EUS-guided cholangiography was published in 1996 by Wiersema et al. [65]. Subsequently in 2006, Giovannini et al. performed a palliative hepaticogastrostomy under EUS guidance in a patient with inoperable hepatic hilar obstruction [66]. EGBD can be achieved by one of two routes: (1) EUS-guided intrahepatic bile duct drainage, where the bile duct is punctured from a transesophageal, transgastric, or transjejunal approach, and (2) EUS-guided extrahepatic bile duct drainage, where the common bile duct is punctured from a transduodenal or a transgastric approach [67]. EUS-guided access and drainage can be either transluminal (endoscopic choledochoduodenostomy) or transpapillary (rendezvous) procedure. Over the past decade, several therapeutic modifications of EGBD have been developed. Both rendezvous and transluminal techniques seem to be equally effective and safe [62]. Based on the current literature, the cumulative success rate is 84–93 %, regardless of the approach, with an overall complication rate of 16–35 % [68]. Khasab et al. compared EGBD to percutaneous drainage (PTBD) in patients with malignant distal biliary obstruction who failed ERCP. Although technical success was higher in the PTBD group (100 % vs. 86.4 %, $p=0.007$), clinical success, stent patency, and survival were equivalent in both groups. The PTBD group, however, was also associated with a higher adverse event rate and higher costs (>2 times) mostly due to a greater number of interventions [69]. Based on these limited, early, compara-

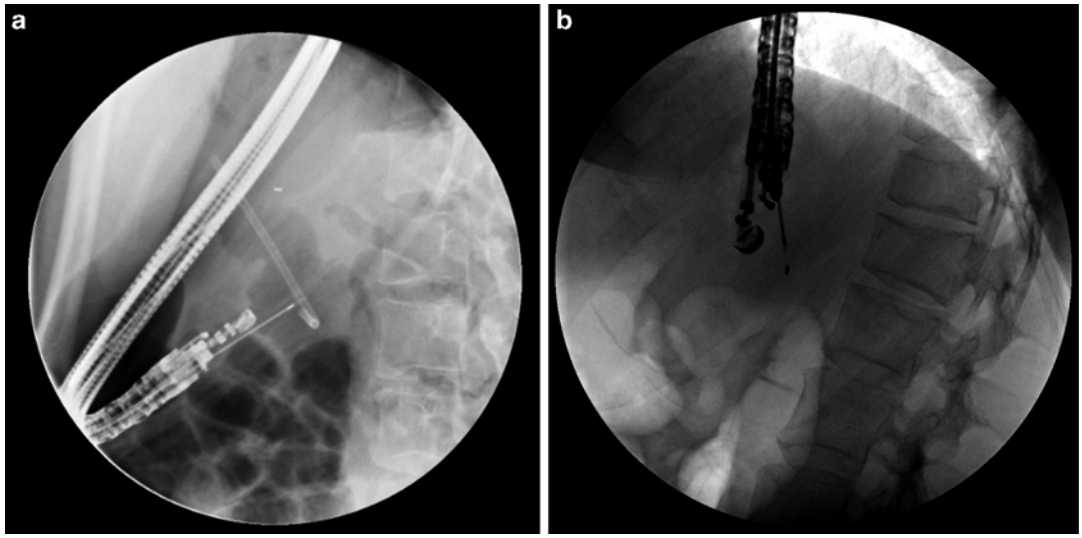

Fig. 3.9 (**a**) Fluoroscopic images of EUS-guided fiducial placement (**b**) final location and placements of fiducials (Courtesy of Dr Shyam Varadarajulu)

to tumors with great accuracy, thereby minimizing damage to the surrounding organs [70]. This is achieved by implantation of fiducials (cylindrical gold seeds) into the target lesion in order to target and track the location of tumor in real time (Fig. 3.9). The standard fiducials measure 3–5 mm in length and 0.8–1.2 mm in diameter. The new smaller, longer fiducial markers are 10 mm in length and 0.35 mm in diameter. To enable appropriate fiducial tracking by the CyberKnife system (Accuracy, Sunnyvale, Calif), it is recommended to place fiducials with "ideal fiducial geometry," i.e., at least 3 fiducials with a minimum interfiducial distance >2 cm, minimum interfiducial angle >15°, and non-collinear placement in the imaging plane [71]. Traditionally, fiducial placement has been attempted either intraoperatively or percutaneously by interventional radiology under CT guidance. In the past few years, EUS has been increasingly used for fiducial placement in patients with inoperable pancreatic cancer [72–74]. With real-time visualization, Doppler imaging capability and the ability to access deeper structures within the GI tract, fiducial delivery can be successfully achieved using a 19-gauge or a 22-gauge needle. In a prospective study by Sanders et al., 51 patients with locally advanced or recurrent pancreatic cancer underwent EUS-guided placement of 0.8 × 5.0 mm fiducials using a 19-gauge needle [73]. Successful placement was achieved in 90 % of patients, with 91 % of patients successfully completing stereotactic body radiotherapy. There was 1 complication of mild pancreatitis occurring in a patient undergoing simultaneous placement of fiducials and celiac plexus neurolysis (CPN) for intractable abdominal pain. 91 % of patients successfully completed stereotactic body radiotherapy. Fiducial migration rate was low (7 %) and no migration-related complications were reported. Technical failures were seen in 4 patients (8 %) with recurrent cancer after pancreaticoduodenectomy.

EUS-Guided Tumor Ablation or Delivery of Anti-tumor Agents

After EUS cemented itself as the primary tool for tissue acquisition via EUS-FNA, the focus shifted to using the FNA needle as a vehicle for drug delivery or therapy. Intuitively, the field of EUS-guided fine-needle injection or FNI makes great sense (Fig. 3.10). FNA needles currently used to perform biopsies of pancreatic masses have been employed as the delivery vehicle or method for performing EUS-guided radiofrequency ablation, cryoablation, and/or EUS-

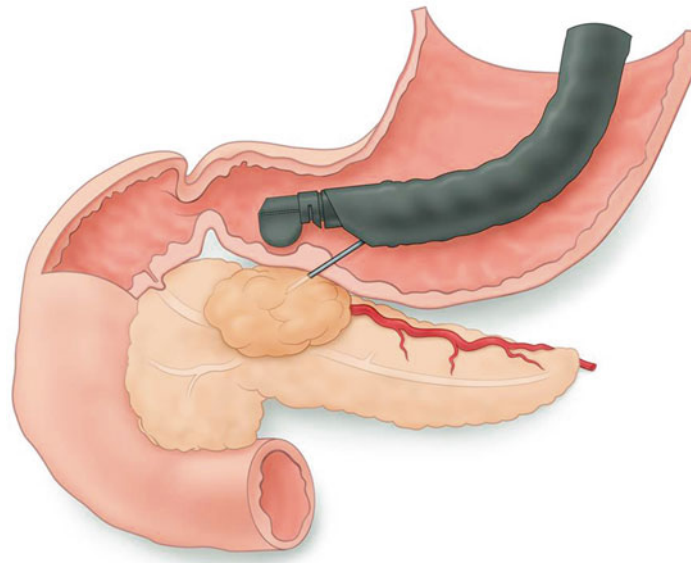

Fig. 3.10 Schema of EUS-guided fine-needle injection (FNI)

guided implantation of brachytherapy seeds [75]. Wallace et al. made several recommendations in their working group document but opined that more human trials will need to be performed to evaluate the different EUS ablative therapies. So far, proof of concept and animal studies offer hope, but human trials are lacking. An area that has made some inroads involves injection of antitumor agents or FNI. The theoretical advantage of EUS-FNI vs. other more invasive techniques is implicit-direct delivery of a cytotoxic agent into a pancreatic mass without having to traverse other tissue or intervening vascular structure organs could minimize toxicity. Perhaps, direct intratumoral injection could overcome the hypovascular milieu of pancreatic cancer and the intense desmoplastic reaction that poses great challenges for systemic chemotherapy. Chang et al. performed the first study exploring this paradigm [76]. They conducted a phase I clinical trial in 8 patients with unresectable pancreatic adenocarcinoma using EUS-guided FNI of an allogenic mixed lymphocyte culture (cytoimplant). The median survival was 13.2 months with two partial responders and one minor response. There were no major toxicities reported. Subsequent studies have incorporated the same concept but utilizing different vectors for EUS-FNI. A few of the studies are summarized in Table 3.1 [76–81]. Although the initial short-term data appear promising, the sustained, long-term results and outcomes remain unsubstantiated. In fact, when Herman et al. conducted a prospective randomized Phase III study comparing standard-of-care to TNFerade plus standard of care for the treatment of locally advanced pancreatic cancer, they found that TNFerade was safe, but not effective for prolonging survival in this cohort of patients. Moreover, EUS-guided injection of TNFerade was a risk factor for inferior disease-free survival [81].

EUS-Guided Celiac Plexus (Block) Neurolysis for Pain

Pancreatic cancer pain can be unbearable and at times, extremely challenging to mitigate. Narcotic analgesics are effective and serve as the mainstay of pain management for most patients. However, in high doses, they commonly induce nausea, delirium, and constipation as well as other adverse effects. CPN is a technique whereby alcohol or phenol, alone or in combination with a local anesthetic (bupivacaine), is injected directly into or near the celiac ganglia to destroy the visceral afferent nociceptors to ameliorate or alleviate chronic abdominal pain, thus serving as an alternative or

Table 3.1 Phase I/II trials of intratumoral endoscopic ultrasound injection (EUS-FNI)

Study and author	Vector	Results
Allogeneic mixed lymphocyte culture (cytoimplant) in PC (Chang et al. [76])	Lymphocyte culture	Phase I promising in 8 pts MS = 13.2 months. Phase II halted
ONYX-015 in PC (Hecht et al. [77])	E1B-55-kDa gene-deleted replication-sensitive adenovirus that preferentially replicates and kills malignant cells	21 pts (no liver mets); 8 sessions over 8 weeks. Final four with gemcitabine. 2-partial regression, 2-minor responses, 6-stable disease, 11-disease progression. 2-sepsis, 2 duodenal perforations
TNFerade in PC (Hect et al. [78])	Second-generation adenovector expressing cDNA to TNF. Maximal TNF secretion to XRT	EUS compared to CT or US ($n = 50$). Combined with 5-FU. Greater locoregional control, longer DFS, stable CA19-9, 45 % resection rate, improved median survival. Ongoing multicenter Phase II/III
BC-819 in unresectable PC (Hanna et al. [79])	DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences	6 patients treated with concurrent chemotherapy plus radiation. 3 patients showed partial response and other 2 were downstaged to undergo surgical resection
Immature dendritic cells (DCs) against PC (Irisawa et al. [80])	Phase I injection DCs into tumor to induce T-cell response against tumor antigens	Media Survival = 9 months in 7 pts with metastatic disease; 1 complete and three partial responses. No adverse events reported
Randomized trial comparing TNFerade with fluorouracil vs. standard of care (Herman et al. [81])	Similar to above, second-generation adenovector	187 patients assigned to standard of care + TNFerade and 90 to standard of care. Median survival was same (10 months) in both arms

additive tool in the management of pain due to pancreatic cancer [82]. With celiac plexus block (CPB), triamcinolone is used rather than the more durable agents. Traditionally, anesthesiologists and radiologists have performed CPN via a posterior approach. EUS offers a distinct, theoretical advantage as the needle used to instill the injectate can be visualized under real-time ultrasound guidance transgastric either in the vicinity of the celiac ganglia (localized by imaging the celiac artery take-off from the aorta), or directly into the ganglion. Antecedent risks such as pneumothorax or even paraplegia could be avoided via this anterior approach. A recent, randomized, controlled trial compared the traditional percutaneous approach for CPB using fluoroscopy vs. EUS-guidance for managing pain due to chronic pancreatitis [83]. Seventy percent of cases noted an improvement when treated via an EUS approach vs. 30 % in the percutaneous group when analyzed using a visual analog score ($p = 0.044$). One of the earliest prospective studies using EUS-CPN for controlling the pain in pancreatic cancer showed great promise as nearly 80 % of the patients reported improvement in pain scores and a decrease in narcotic usage [84]. This initial excitement led to working group document that recommended further randomized and sham controlled studies to better assess the role of EUS-CPN for the management of pain in pancreatic cancer [85]. Wyse et al. randomized 96 patients with advanced pancreatic cancer to early EUS-guided CPN vs. conventional pain management and found that the early EUS-CPN-treated patients were afforded greater pain relief at 3 months [86]. A recent, systematic review supports the overall and early use of EUS-CPN for the management of pain in pancreatic cancer [87].

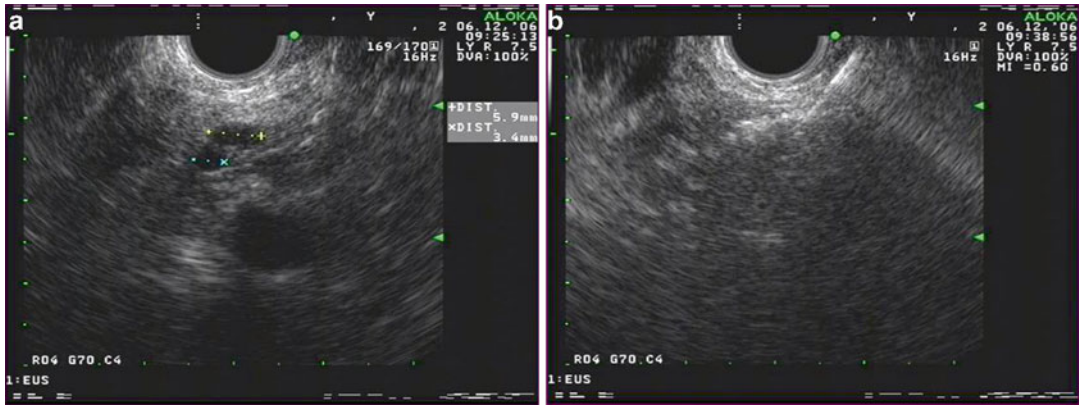

Fig. 3.11 EUS image of (**a**) celiac ganglion (**b**) celiac plexus neurolysis into the celiac ganglion using a 19-g needle

Could refinement in technique by directly injecting into the celiac ganglion more effectively ameliorate the pain in pancreatic cancer (Fig. 3.11)? The revelation that the celiac ganglion can be visualized and targeted via EUS-FNA safely, subsequently led to studies citing this approach as more efficacious for controlling pain in pancreatic cancer [88, 89]. Although limited by the number of patients and duration of follow-up, Levy and colleagues reported a nearly 95 % complete or partial response with regard to pain in 18 patients with pancreatic cancer. Ascunce et al. performed a retrospective analysis of 64 patients with pancreatic cancer and found that visualization of the celiac ganglia was the best predictor of response to EUS-CPN in pancreatic cancer (OR 15.7; $p<0.001$). Unfortunately, untoward side effects and complications have ranged from the mild (diarrhea, abdominal pain, hypotension) to serious (bleeding, abscess, ischemia, and even death) [90].

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4 Endoscopic and Percutaneous Biliary Drainage Procedures: Role in Preoperative Management, Diagnosis, and Palliation

Milton T. Smith

Introduction

Biliary drainage procedures for management of obstructive jaundice secondary to pancreatic cancer are frequently performed in clinical practice. Pancreatic cancer accounts for approximately 3 % of all cancers seen in the USA, and it is estimated that approximately 48,960 new cases will be seen in the USA in 2015 with 40,560 deaths [1]. This potentially fatal disease accounts for about 7 % of cancer deaths and is the fourth leading cause of cancer-related deaths among men and women [2].

Patients with pancreatic cancer often present with biliary obstruction as approximately 80 % of these neoplasms occur in the head of the gland. Jaundice, with or without pain, is seen in over half of patients who present with resectable, borderline resectable, or locally advanced disease [3, 4]. In other patients, jaundice develops later in the course as the disease progresses. Jaundice is typically a late finding when the primary tumor is located in the tail of the pancreas and often reflects metastatic disease. Surgical resection offers the only potential for curative treatment. However, only 15–30 % of patients are candidates for curative-intent surgery as the majority present at a more advanced stage and have either locally advanced or metastatic disease.

Obstructive jaundice may result in severe pruritus, progressive hepatocellular dysfunction, coagulopathy, malabsorption, and cholangitis [5]. Biliary decompression may be accomplished by surgical, radiologic, or endoscopic techniques. Although these modalities are equally effective in relieving biliary obstruction, endoscopic drainage via placement of a biliary stent (plastic or metal) during ERCP is generally considered safer, less invasive, and is preferred for most patients when technically feasible [6, 7]. PBD has been advocated largely in an attempt to reduce postoperative complications following surgical resections. This is based upon the rationale that pathophysiological derangements seen in the setting of biliary obstruction could potentially be reversed by restoring bile flow and ultimately translate into improved clinical outcomes.

Despite the fact that endoscopic and percutaneous drainage procedures are technically successful in 90–95 % of cases [5], the role of PBD remains controversial. Clinical studies have reported both beneficial and adverse effects, and most studies have advised against routine PBD due to the potential for procedure-related complications such as bleeding, perforation, pancreatitis, bacterial colonization of bile, and complications of stent

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occlusion such as cholangitis. Nevertheless, PBD is often considered necessary in clinical practice for selected patients. Most clinicians recommend PBD for the following clinical scenarios: (1) Patients with resectable disease who have surgery delayed for logistical reasons, (2) The resectability status may not be known with certainty at the time of initial ERCP, (3) To facilitate neoadjuvant chemoradiation in patients with borderline resectable cancer, (4) Management of cholangitis (or severe pruritus), (5) Palliation of jaundice in patients with unresectable disease. This chapter will focus on biliary drainage procedures and their role in management, diagnosis, and palliation of patients with obstructive jaundice due to pancreatic cancer.

Role of ERCP in the Diagnosis of Pancreatic Cancer

ERCP is a highly sensitive modality for visualization of the biliary tree and pancreatic ducts. It also provides the opportunity to obtain tissue samples and perform therapeutic maneuvers. However, with advances in cross-sectional imaging and endoscopic ultrasound (EUS), the role of ERCP in patients with suspected pancreatic cancer has evolved into a mainly therapeutic modality for patients with biliary obstruction and require decompression. ERCP alone provides little staging information for pancreatic cancer.

Certain endoscopic and radiographic features observed during ERCP should alert the endoscopist to the possibility of pancreatic cancer. The presence of mucus extrusion from the papillary orifice is compatible with a main duct intraductal papillary mucinous neoplasm (IPMN), a condition that may lead to the development of pancreatic ductal adenocarcinoma. The pancreatogram in such cases might also reveal intraductal mucin which is seen as a filling defect within the pancreatic duct (Fig. 4.1). Direct invasion of the ampulla or duodenal wall caused by a neoplasm in the head of the pancreas is sometimes seen endoscopically. Standard forceps biopsies may yield a diagnosis in these cases (Fig. 4.2). Mass lesions in the head of the pancreas often cause simultaneous obstruction of the common duct and pancreatic duct (i.e., double-duct sign). At ERCP, this appears as a focal stricture of the common bile duct and pancreatic duct, typically

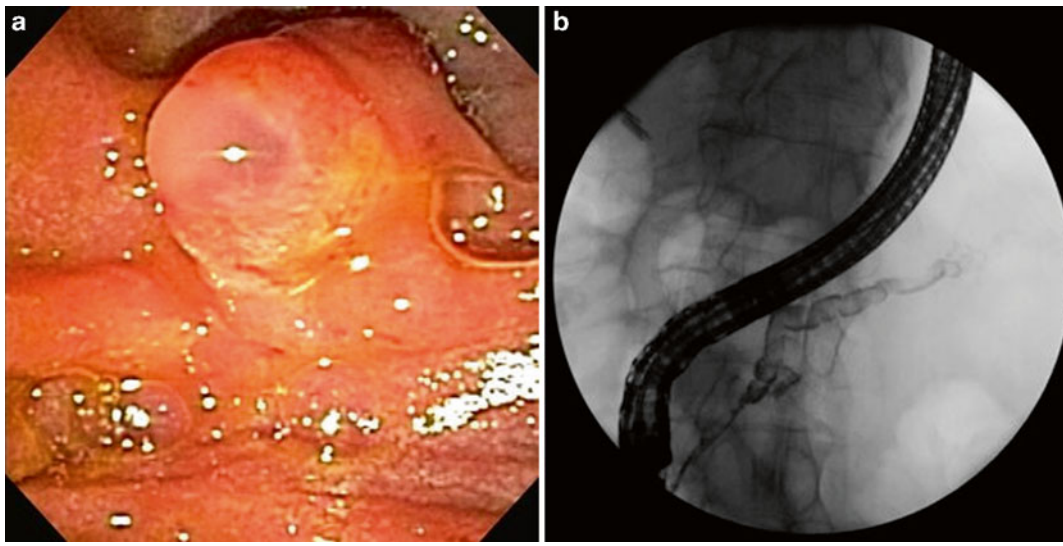

Fig. 4.1 (**a**) Endoscopic photograph of thick mucus extruding from the orifice of the major papilla. This finding is compatible with main-duct intraductal papillary neoplasm, a condition strongly associated with pancreatic ductal adenocarcinoma. (**b**) Pancreatogram revealing a long cast-like filling defect in the main pancreatic duct, reflecting the presence of intraductal mucus. Also note the presence of a ductal stricture in the head of the pancreas

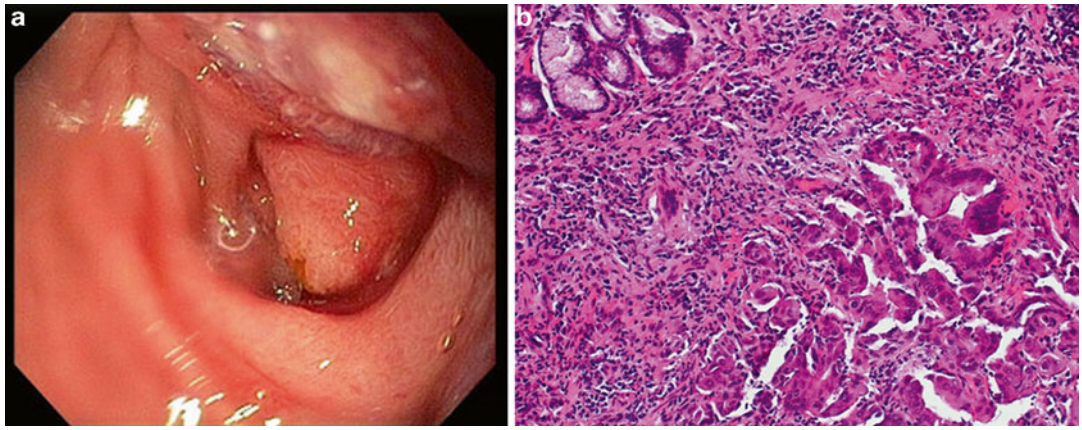

Fig. 4.2 (**a**) Endoscopic photograph of direct invasion of the duodenal wall caused by a pancreatic head mass. Note the uninvolved orifice of the major papilla seen downstream. (**b**) Standard forceps biopsies confirmed adenocarcinoma invading the duodenal wall

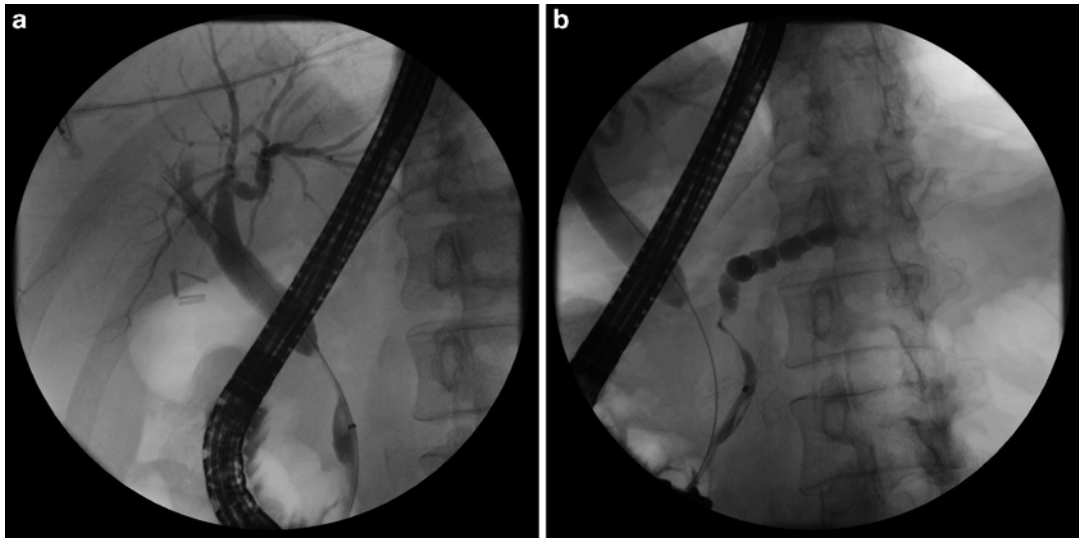

Fig. 4.3 (**a**) Double-duct sign. Cholangiogram revealing a common bile duct stricture with upstream dilation. (**b**) Pancreatogram revealing a long irregular stricture in the head of the pancreas with upstream dilation. Simultaneous obstruction of the common duct and pancreatic duct is highly suggestive of a mass lesion in the head of the pancreas

with associated upstream dilation of both ducts (Fig. 4.3). Other features of a stricture which are suggestive of malignancy include an abrupt cut-off of the pancreatic duct, a ragged contour, or stricture length >1 cm. These radiographic features are helpful but nondiagnostic and may occasionally be found in benign conditions such as chronic pancreatitis. The presence of a stricture in the pancreatic duct and/or bile duct must be interpreted in clinical context, but generally leads to tissue sampling during ERCP if the diagnosis remains in question as a definitive diagnosis of malignancy requires tissue confirmation.

Tissue sampling techniques during ERCP include brush cytology, forceps biopsy, aspiration of bile or pancreatic juice for cytology, or a

combination. In patients in whom a plastic stent has already been placed, the stent can be spun and the cells obtained can be evaluated [8]. Exfoliated malignant cells may be adherent to the surface of the stent as they become entrapped within biofilm and sludge. The sensitivity rate for ERCP-directed brush cytology or biopsy is 30–50 %, with a combination of techniques achieving sensitivity rates of approximately 70 % [9, 10]. This is considerably less than EUS-guided fine needle aspiration (FNA) which has a sensitivity of approximately 85–90 % for the diagnosis of pancreatic cancer [11]. Several studies have shown that diagnostic yield during ERCP can be increased by using a combination of different tissue sampling methods [12, 13]. Unfortunately, the negative predictive value in tissue sampling during ERCP using a combination of techniques is nearly 40 % [12].

Although aspiration of bile or pancreatic juice is simple to perform, fluid cytology alone has a low sensitivity and is not performed by most endoscopists. Fluid specimens are often acellular, likely due to the desmoplastic nature of certain tumors or failure to invade the ductal epithelium. Techniques to increase tumor exfoliation prior to collecting specimens, such as stricture dilation or saline irrigation, have not demonstrated increased cancer detection rates in prospective comparative trials [12]. Forceps biopsies have a higher yield, but generally require a sphincterotomy to gain access to the bile duct or pancreas. When performing forceps biopsies, it may be helpful to first place a guidewire across the stricture to maintain access and for use as a guide for cannulation and positioning of the biopsy forceps (Fig. 4.4). Performing intraluminal forceps biopsies during ERCP can be technically challenging as the device cannot be passed over a guidewire. It may also increase the risks of the procedure, including bleeding, pancreatitis, and perforation. By comparison, biliary brush cytology is relatively easy to perform as the brush passes over a prepositioned guidewire to acquire a specimen within the stricture. The overall technical success rate of biliary brush cytology is >90 %. Brush cytology in the pancreatic duct is sometimes helpful but is frequently more difficult to perform. Pancreatic cancer often causes tight strictures of the main pancreatic duct which prohibit passage of the brush through the tumor in greater than 25 % of patients [12] (Fig. 4.4). Because of the aforementioned challenges, most practitioners perform biliary brush cytology alone, which has sensitivity as low as 30 %. Although the sensitivity of brush cytology or forceps biopsy alone is suboptimal, both techniques are almost 100 % specific [13]. Advanced techniques such as digital image analysis may enhance the accuracy of routine cytology [14], but is not widely available. Additional methods to improve the diagnostic yield such as the molecular analysis of the components of pancreatic juice and bile remain experimental [9, 15, 16]. Although the overall performance of tissue sampling techniques during ERCP in patients with suspected pancreatic cancer is significantly lower than EUS-FNA, it remains an important modality and should be performed whenever a diagnosis has not been established at the time of the procedure.

Rationale for Preoperative Biliary Drainage

Historically, major hepatobiliary surgical procedures in patients with obstructive jaundice have been associated with significant morbidity and mortality, largely due to the development of postoperative complications such as sepsis, bleeding disorders, and renal failure. Biliary obstruction has been regarded as a risk factor that can worsen the outcome after surgery [17]. The primary rationale of PBD for patients with biliary obstruction due to pancreatic cancer is to reduce the risk of postoperative complications. The concept of PBD was introduced by A.O. Whipple and colleagues in 1935 when they published one of the first case series of PBD for patients with periampullary cancer [18]. The two-staged technique involved performing a preliminary open biliary diversion procedure (cholecystogastrostomy) to reduce jaundice, followed by resection of the primary tumor at a later stage, depending on the severity of jaundice. The goal of this approach was to optimize the overall physical status of the patient prior to definitive resection.

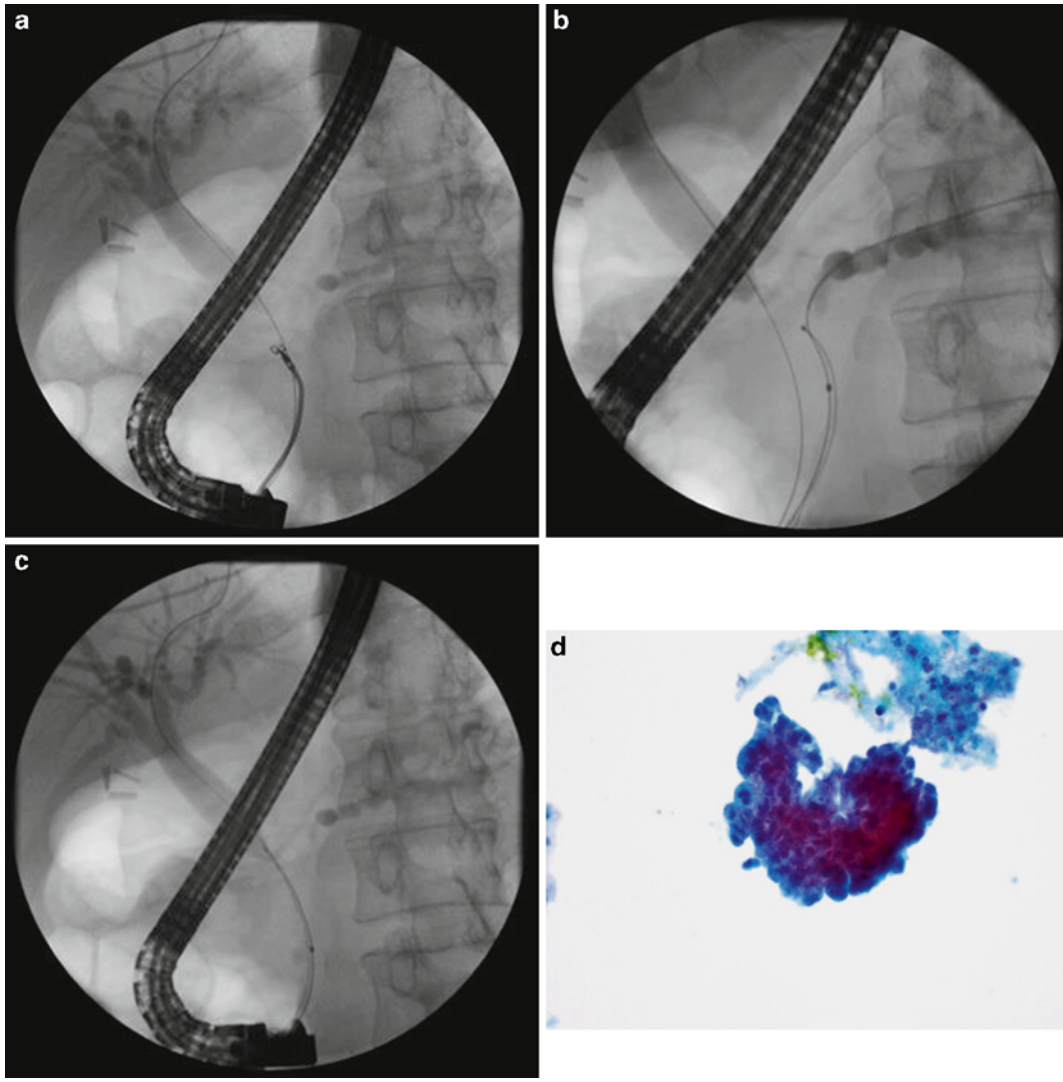

Fig. 4.4 (**a**) Biliary forceps biopsy. A guidewire passed through the biliary stricture is used as a guide for cannulation and positioning of the biopsy forceps. (**b**) Pancreatic duct brush cytology. A second guidewire has been passed through the pancreatic duct stricture and is used to position the cytology brush. Brushings within pancreatic duct may be challenging to perform due to the tight nature of the stricture. (**c**) Biliary brush cytology. A cytology brush has been passed over a prepositioned guidewire to acquire a specimen within the stricture. (**d**) Photomicrograph of a specimen obtained during biliary brush cytology revealing crowding and overlapping of cells, compatible with adenocarcinoma

Biliary obstruction is associated with several deleterious effects. Animal studies have shown that obstructive jaundice leads to a proinflammatory state resulting from portal and systemic endotoxemia [19]. Decreased bile in the intestinal lumen causes increased permeability of the intestinal mucosal barrier, promoting bacterial translocation and the occurrence of endotoxemia [20]. Systemic endotoxemia leads to impaired cellular immunity and increased concentrations of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-8 (IL-8), and tumor necrosis factor (TNF) [21–23]. The overall effects of obstructive jaundice in

humans on endotoxin and cytokines may be different from those seen in animal models [24]. Biliary obstruction also causes a reduction in hepatic reticuloendothelial system function leading to a diminished clearance of endotoxin by Kupffer cells [24, 25]. Persistent elevation of cytokines has been associated with protein calorie depletion, a factor associated with higher surgical complications which could potentially be reversed by biliary decompression. Malignant biliary obstruction may also adversely affect coagulation due to bile acid-induced hepatocyte damage [26] as well as impaired hepatic synthesis of vitamin K-dependent coagulation factors secondary to reduced vitamin K absorption from the intestine. Despite these effects favoring bleeding complications, a recent study has shown that patients with severe biliary obstruction may also develop a procoagulant state which was almost completely reversed by preoperative endoscopic biliary drainage [27]. In addition to impairment of immune function and coagulopathy, biliary obstruction is also associated with renal dysfunction. Cholestatic jaundice is known to have deleterious effects on cardiovascular function, blood volume, and vascular reactivity. The overall effect of obstructive jaundice predisposes the kidney to prerenal failure and acute tubular necrosis. Most evidence suggests that the constituents of bile (cholesterol, bilirubin, bile acids) do not exert a direct nephrotoxic effect [28]. A multivariate analysis has shown that renal dysfunction in patients with obstructive jaundice is associated with the degree of biliary obstruction as well as the age of the patient [29]. Biliary obstruction may also be associated with impaired myocardial function and is associated with increased plasma levels of atrial natriuretic peptide (ANP). Internal biliary drainage results in improvement in cardiac function and normalization of ANP [30].

The adverse effects of biliary obstruction on multiple organ systems and immune function may adversely impact the outcome after major surgery for patients with pancreas cancer. Preoperative biliary drainage has the potential to improve surgical outcomes by reversing the detrimental effects via restoration of bile flow.

Methods of Preoperative Biliary Drainage

Endoscopic stent placement and percutaneous biliary drainage have largely replaced surgical biliary bypass for management of biliary obstruction due to pancreatic cancer. These techniques are generally considered less invasive, less expensive, and have a shorter recovery time as compared to surgical procedures. The choice between endoscopic vs. percutaneous biliary drainage is often a matter of a local expertise and patient anatomy, although endoscopic stent placement is preferred whenever possible due to fewer procedure-associated complications [31]. Percutaneous biliary drainage is more often used when endoscopic stent placement is unsuccessful or not technically possible due to altered anatomy (e.g., duodenal obstruction, tumor invasion of the ampulla, or previous surgical bypass procedures).

Percutaneous Biliary Drainage

Percutaneous transhepatic biliary drainage (PTBD) was introduced in the 1960s and was the treatment of choice for biliary drainage for over two decades [32, 33]. PTBD drainage is most often performed using fluoroscopic guidance although ultrasound can be helpful for the initial puncture when the bile ducts are dilated [34]. The technique involves passing a skinny needle (21 or 22 gauge) through the hepatic parenchyma until reaching a dilated intrahepatic bile duct. A percutaneous cholangiogram is performed by injecting contrast as the needle is slowly withdrawn, followed by passage of a small diameter (0.018 in.) guidewire to secure the position in the biliary tree. Once the dilated duct has been accessed with the needle, the needle is exchanged for a coaxial system to upsize the 0.018-in. access guidewire to a larger guidewire (e.g., 0.035 or 0.038 in.) which is more stable and can be used for further interventions.

PTBD can provide biliary drainage in three ways. The simplest of these is external drainage which involves decompressing the biliary tree through a percutaneous tube which exits the skin,

but the intraductal tip is left upstream to the site of biliary obstruction. The method is typically used when a tight stricture cannot be traversed with a guidewire after percutaneous access to the biliary tree has been achieved. A major disadvantage of external drainage is the fact that bile flow to the duodenum is not restored. For internal–external drainage, a directional catheter is inserted through the percutaneous sheath and advanced over a hydrophilic guidewire through the biliary obstruction and into the duodenum. The catheter can then be exchanged over a stiffer guidewire (e.g., Amplatz) for a multiside-hole drainage catheter which is passed through the stricture into the duodenum. The internal–external catheter allows bile to drain externally into a bag and/or internally into the duodenum, thereby preserving the normal enterohepatic circulation of bile (Fig. 4.5). The third technique establishes internal drainage by percutaneous placement of a plastic or self-expandable metal stent (SEMS) across the biliary stricture. Recent studies have shown percutaneous SEMS placement to be a safe and effective technique [35–38]. Although it is common practice to establish initial internal–external drainage prior to SEMS placement, some experienced centers have reported good results with percutaneous SEMS insertion as a single-stage procedure [35, 36]. A retrospective study from the UK reported an overall technical success rate of 79 % among 67 patients undergoing percutaneous short SEMS placement for biliary obstruction due to pancreatic or periampullary tumors [35]. The complication rate was 9.4 % although all complications were managed conservatively and none precluded subsequent surgery.

One disadvantage of PTBD is that it cannot be used in the presence of moderate or severe ascites [39]. PTBDs can be cumbersome for patients to manage and require significant maintenance. External drains require periodic emptying, flushing of the drain, and drain exchanges to prevent occlusion [40]. PTBDs can also be prone to leakage, dislodgement, and complications such as hemobilia and infection. A recent prospective study involving 109 patients with advanced malignancy showed that PTBD improved pruritus and hyperbilirubinemia, but not overall quality of life [41]. Despite potential drawbacks, PTBD continues to have an important role for management of biliary obstruction, especially when ERCP is unsuccessful [42].

Endoscopic Biliary Drainage

The most common and generally preferred method of achieving preoperative biliary drainage is by ERCP with stent placement. Endoscopic stents are often used as a bridge to surgery for patients with resectable or borderline resectable disease as well as for long-term palliation for unresectable pancreatic cancer. The main advantage of an endoscopic approach over PTBD is the avoidance of skin and liver punctures as well as the risk of tumor seeding which may occur along the catheter and to the skin [43]. Recent meta-analyses have suggested that endoscopic stenting provides superior results to open surgical bypass in patients with distal biliary obstruction due to pancreatic cancer [7, 44]. Biliary drainage may be achieved using either plastic stents or SEMS and it is now clear that stent luminal diameter is a critical factor for both types as the risk of stent occlusion correlates with stent diameter. In general, wider diameter stents have a lower risk of short-term occlusion, whether plastic or metal.

Plastic biliary stents have been used since their development in the 1980s and are now commercially available in a wide variety of diameters, lengths, and designs (Fig. 4.6). They may be composed of various materials including polyethylene, polyurethane, and Teflon. Plastic biliary stents are available in diameters ranging from 5 to 12 Fr and lengths from 1 to 18 cm [45]. The primary advantages of using plastic stents for malignant biliary obstruction are that they are effective, have lower costs, and are easily removed or exchanged. Plastic stents are often selected when a diagnosis has not been established or the patient's resectability status is unknown at the time of initial endoscopic treatment. The major disadvantage of plastic stents is that they have a high rate of occlusion due to formation of bacterial biofilm, sludge, as well as dietary fibers [46] (Fig. 4.7); this leads to the

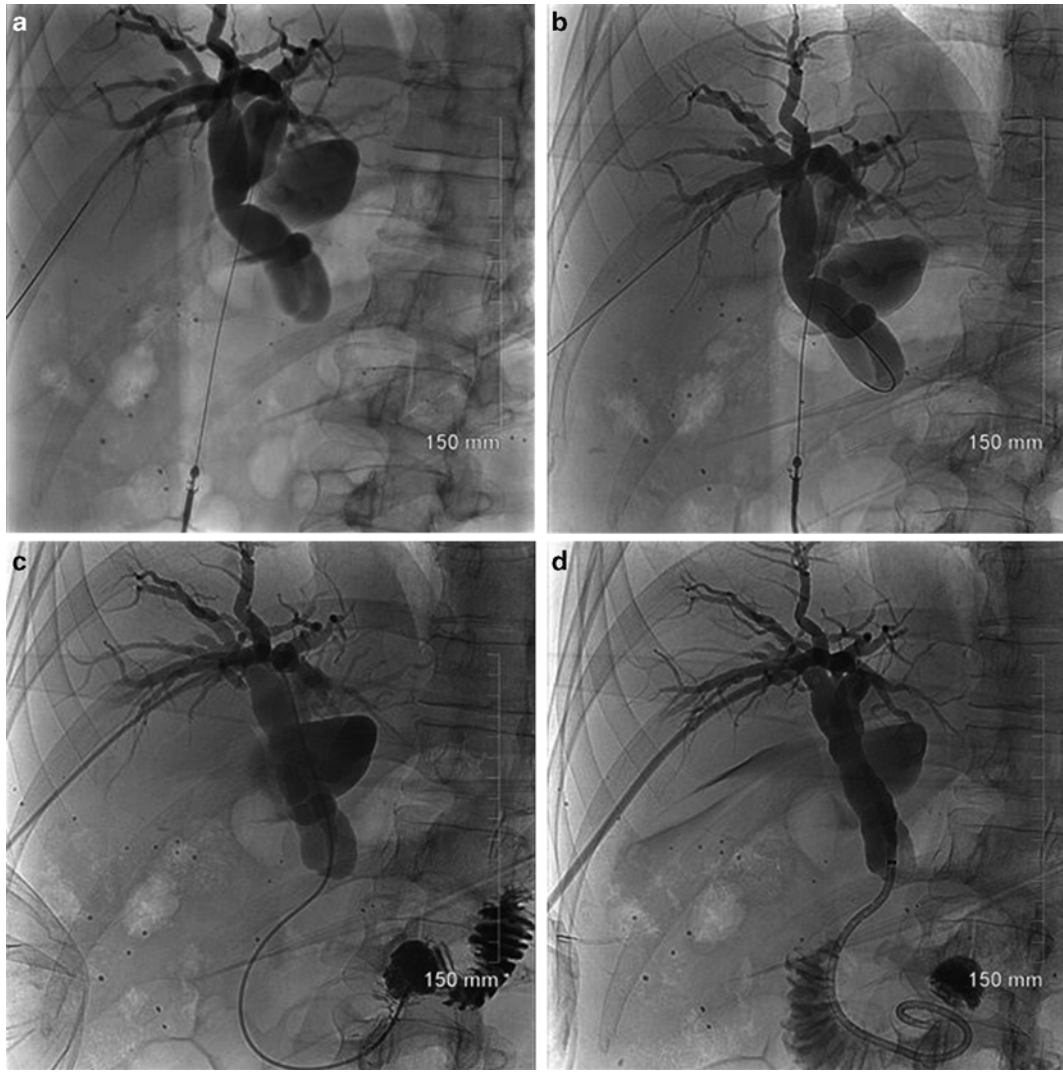

Fig. 4.5 (**a**) The patient is a 60-year-old male with borderline resectable pancreatic head cancer who underwent unsuccessful ERCP due to failed bile duct cannulation. A percutaneous transhepatic cholangiogram was performed by injection of contrast through a 22 gauge Chiba needle. Needles are shown entering left and right intrahepatic ducts. (**b**) Initial attempts to pass a guidewire through the high-grade bile duct stricture in the head of the pancreas were unsuccessful. No contrast flowed through the stricture. (**c**) A stiff 0.035 in. hydrophilic guidewire and 5 Fr catheter were ultimately passed through the stricture into the duodenum. (**d**) Following placement of a 0.035 Amplatz guidewire and dilation of the tract to 10 Fr, a 10 Fr multiside hole internal-external drainage catheter was placed with tip reaching the transverse duodenum

need for repeat procedures and stents exchanges. In general, 7 Fr plastic stents remain patent for approximately 8 weeks whereas 10 Fr plastic stents remain patent for an average of 3–5 months [47]. It is important to note that plastic biliary stents often do not maintain patency during the time required for most patients to complete neoadjuvant chemoradiotherapy for pancreatic cancer. A recent retrospective study reported that among 49 patients treated with plastic stents who were undergoing neoadjuvant therapy, 55 % required repeat ERCP for stent malfunction at a median of 82.5 days after initial stent placement [48]. Studies evaluating stent designs have

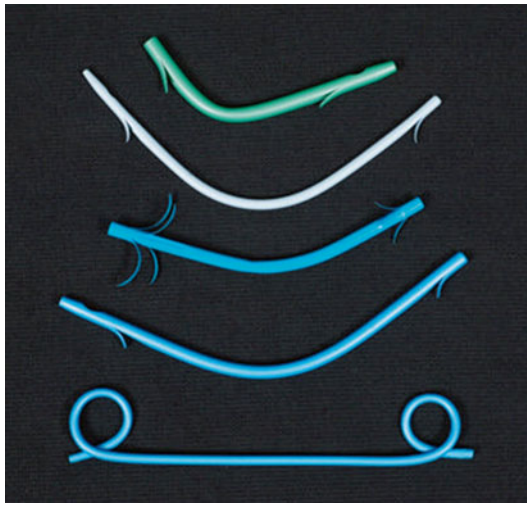

Fig. 4.6 Various plastic biliary stents. Plastic stents are available in a variety of diameters, lengths, and designs and may be composed of different materials. Stents which have a wider luminal diameter generally remain patent longer

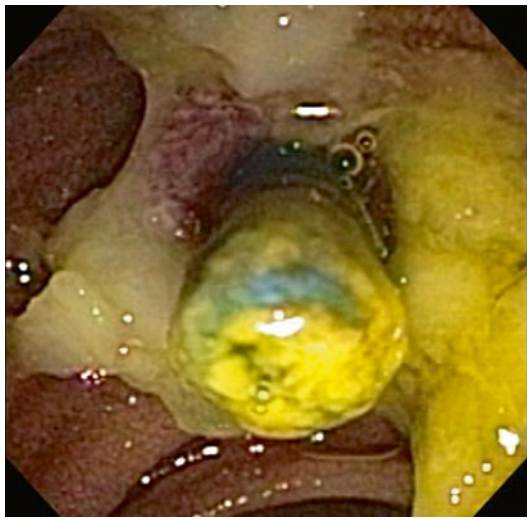

Fig. 4.7 Endoscopic photograph of an occluded plastic biliary stent. Plastic stents occlude due to the formation of bacterial biofilm and biliary sludge. High occlusion rates is a limiting factor in the use of plastic stents for preoperative biliary decompression for pancreatic cancer

compared stents composed of Teflon without side holes to standard polyethylene stents with side holes. No difference in patency rates was found based upon stent composition or design [49, 50]. Although it is generally accepted that larger diameter plastic stents (10 Fr or greater) have a longer patency than smaller diameter stents, a study comparing 10–11.5 Fr stents found no difference in patency rates [51]. A Cochrane meta-analysis found that choleretic agents such as ursodeoxycholic acid (UDCA) and/or antibiotics do not appear to improve plastic stent patency rates [52].

SEMS are now widely used for management of malignant biliary obstruction. As with plastic stents, SEMS are available in a variety sizes and designs (Fig. 4.8). Multiple studies have shown that when compared to plastic stents, SEMS have a superior patency rate when used for preoperative biliary decompression due to pancreatic cancer [7, 48, 53–58] (Fig. 4.9). The improved patency of SEMS relates to the fact that when fully deployed, SEMS have a roughly threefold wider luminal diameter than most plastic stents. Longer stent patency is especially important as more centers adopt neoadjuvant therapy as a standard of preoperative care. Stent occlusions during this period can result in severe complications such as cholangitis as well as interruptions in therapy, hospitalizations, unplanned procedures, and delays in eventual surgery [59]. In a recent prospective study evaluating SEMS in 55 patients undergoing neoadjuvant therapy for pancreatic cancer, only 15 % experienced stents malfunctioned by 260 days after placement [60]. This compares favorably to a 55 % stent malfunction rate when plastic stents were used for a similar patient population [48]. Another retrospective study evaluating plastic stents and SEMS for preoperative biliary decompression reported a 39 % stent dysfunction rate for those who received plastic stents compared to no stent dysfunction for those who received an SEMS [54]. Adams et al. evaluated stent complications among 52 patients who underwent placement of either a plastic stent or SEMS to receive neoadjuvant therapy for pancreatic cancer [57]. The complication rate was nearly seven times higher with plastic stents than with SEMS. Moreover, the rate of hospitalization for stent-related complications was threefold higher in the plastic stent group than the SEMS group.

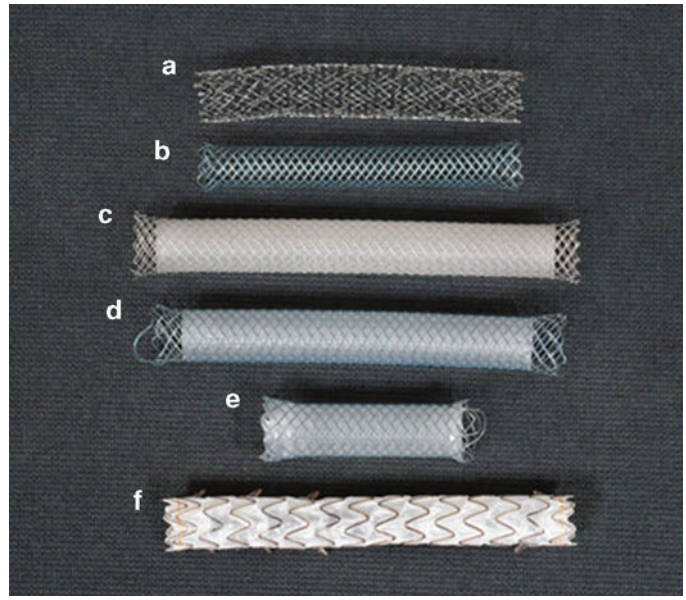

Fig. 4.8 Various self-expandable metal biliary stents. (**a**) Uncovered Zilver (Cook) (**b**) uncovered Wallflex (Boston Scientific) (**c**) partially covered Wallstent (Boston Scientific) (**d**) partially covered Wallflex (Boston Scientific) (**e**) fully covered Wallflex (Boston Scientific) (**f**) fully covered Viabil (ConMed)

One factor that led to the initial use of plastic stents for preoperative biliary decompression was the concern that uncovered SEMS could potentially cause technical difficulties with transecting the bile duct and creating a biliary anastomosis during subsequent pancreaticoduodenectomy. Studies have now shown that placement of a short-length SEMS (typically 4–6 cm length) does not interfere with the outcome of surgery [5, 54, 61–63]. Siddiqui et al. reported the outcome of 241 patients with resectable or borderline resectable disease who underwent preoperative SEMS placement [63]. Uncovered, partially covered, and fully covered SEMS were used. Ultimately, 166 patients underwent curative-intent surgery without any observed technical difficulties during surgery due to the presence of an SEMS. Similarly, Mullen et al. found no difference in intraoperative or postoperative complications, or length of hospital stay among 29 patients who underwent pancreaticoduodenectomy after SEMS placement compared to those who had plastic stents (n-141), no stent (n-92), or biliary bypass (n-10) prior to surgery [64]. It is advisable during stent placement to use the shortest length SEMS possible to bridge the stricture with care taken to leave an adequate length of common hepatic duct un-stented (ideally 2 cm) to simplify any future surgical anastomosis, especially if using an uncovered SEMS. The choice between plastic stent vs. SEMS may ultimately rely on other factors such as cost, expected survival length, and certainty of diagnosis at the time of initial ERCP.

Although SEMS remain patent longer than plastic stents, they are also at risk for occlusion due to tumor ingrowth through the mesh interstices, overgrowth beyond the ends of the stent, or due to a hyperplastic response of normal tissue caused by the stent (Fig. 4.10). For this reason, SEMS were developed which are partially or fully covered with a goal of improving patency by preventing tumor and tissue ingrowth. Coverings include material made of polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene/fluorinated ethylene propylene (ePTFE/FEP), or silicone membranes. The covering may be on the exterior or interior of the stent. Some fully covered stents have fenestrations in the cover without exposing the metal wires. Unfortunately, covered stents may also occlude due to stent migration, tumor/tissue overgrowth, tumor ingrowth as the covering deteriorates over time, or possibly due to food debris [40]. Reflux of duodenal contents into SEMS is also known to occur [65] and could potentially cause problems

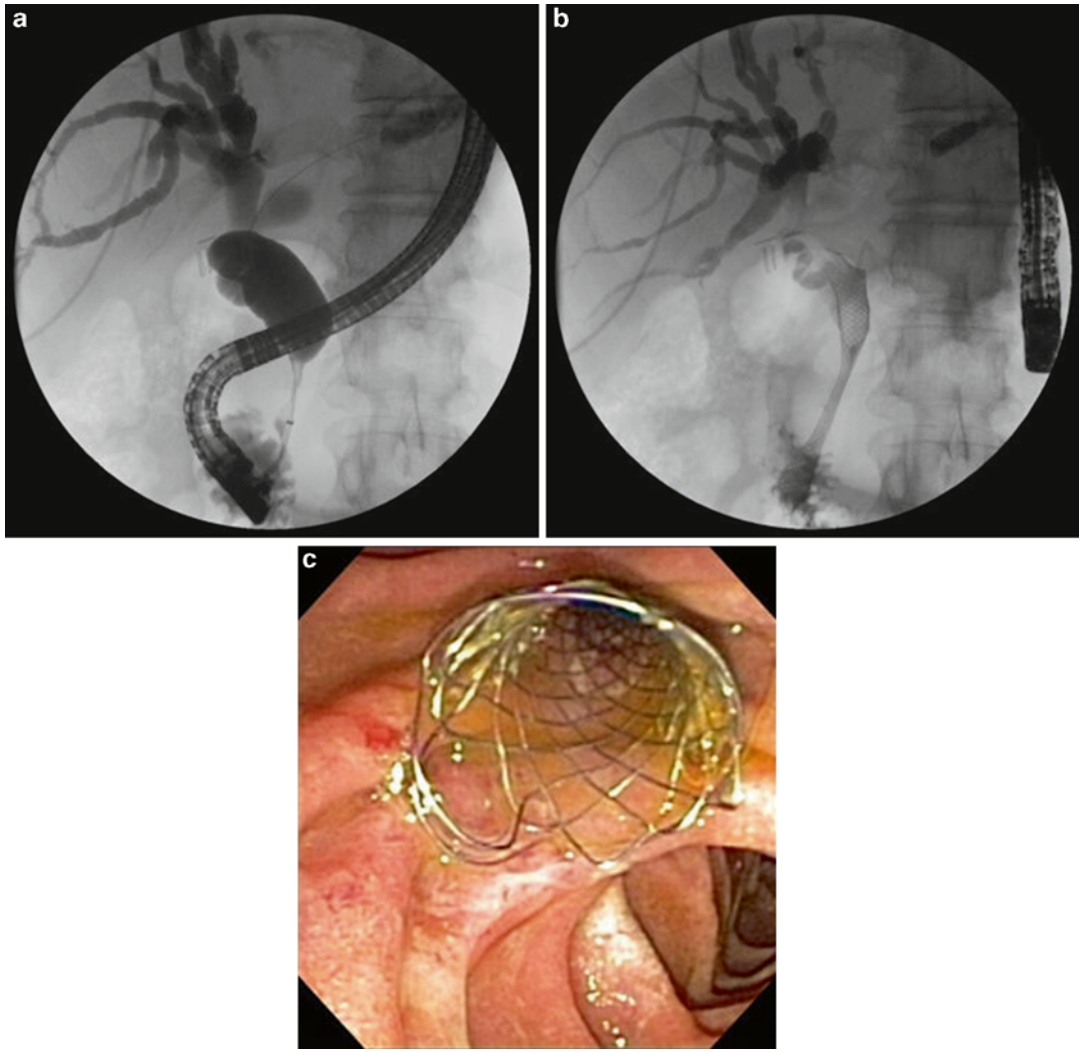

Fig. 4.9 (**a**) A patient with borderline resectable pancreatic cancer underwent ERCP for management of obstructive jaundice prior to neoadjuvant therapy. The cholangiogram revealed a distal common bile duct stricture with upstream dilation. (**b**) A 10×60 mm biliary self-expandable metal stent was placed with subsequent resolution of jaundice. (**c**) Endophoto of a biliary self-expandable metal stent following placement

in some patients. One of the advantages of uncovered SEMS, which has been shown in several studies, is their low migration rate (0–2 %) [56, 66, 67]. This is presumably due to embedding of the stent into the wall of the bile duct after deployment. Covered SEMS have a higher migration rate of approximately 6–8 %. Partially and fully covered stents have the advantage that they can be repositioned or fully removed using a rat-tooth forceps or snare [45]. SEMS are available in 6, 8, and 10 mm diameters when fully deployed, which is a key feature in determining the risk of occlusion. A large prospective multicenter study randomized 241 patients with malignant biliary strictures to receive uncovered SEMS of different designs in two diameters (i.e., 6 mm Zilver, 10 mm Zilver, or 10 mm Wallflex). SEMS occlusions were much more frequent with a 6-mm diameter SEMS and equivalent in the two 10-mm arms despite major differences in stent design, material, and expansion, suggesting that diameter is the critical feature [68]. Similarly, Yang et al.

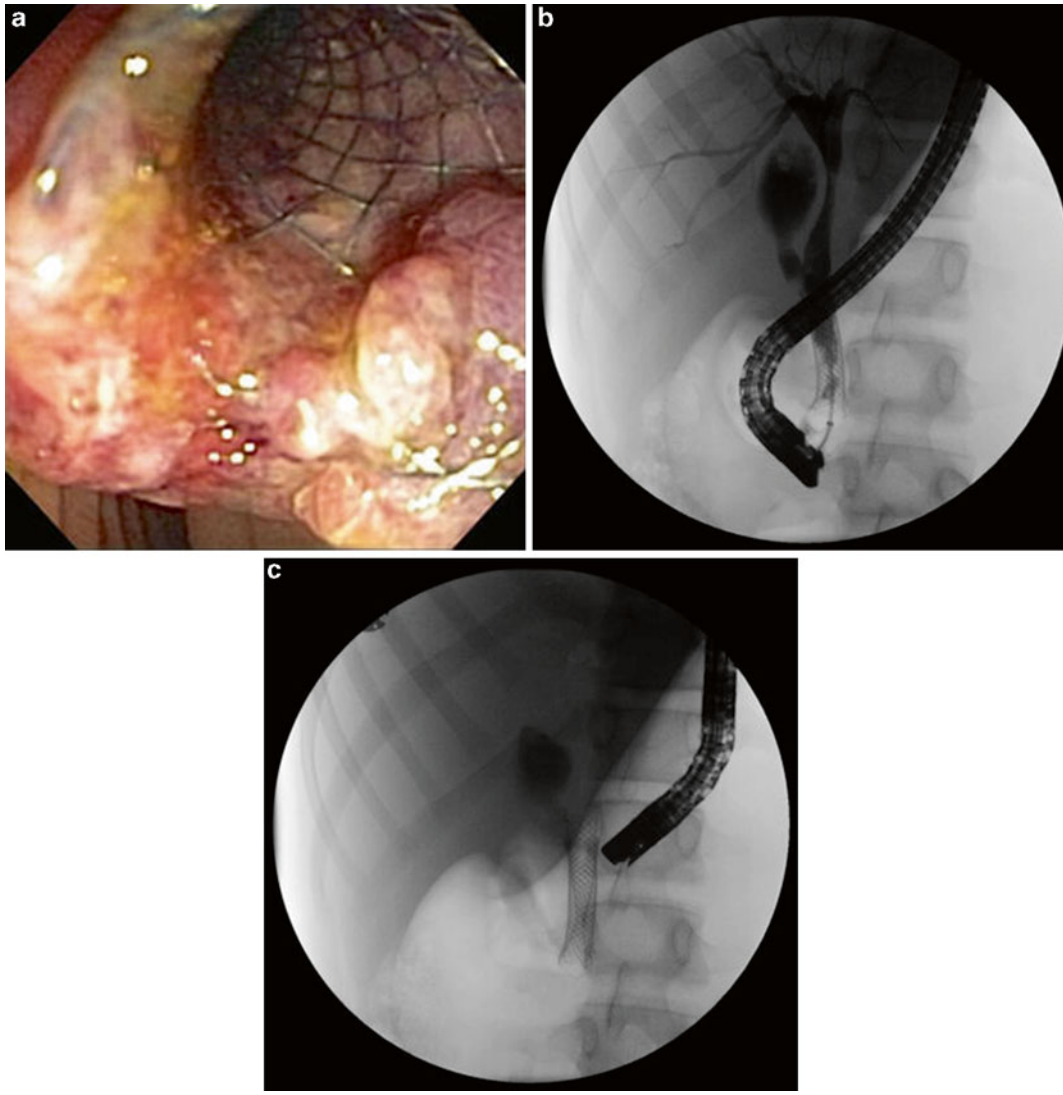

Fig. 4.10 (**a**) Endoscopic photograph demonstrating tissue overgrowth at the duodenal end of a biliary self-expandable metal stent. (**b**) Balloon occlusion cholangiogram revealing a biliary stricture caused by tumor or tissue ingrowth through the interstices of the existing metal biliary stent. (**c**) A second SEMS was deployed within the existing SEMS with resolution of biliary obstruction

showed no significant difference in the rate of occlusion when using uncovered SEMS of equal diameter, but different stent design [69].

Studies comparing the differences in patency rates between covered and uncovered SEMS in patients with malignant distal bile duct obstruction have shown conflicting results. For example, two randomized multicenter trials found no difference in patency rates [70, 71]. Another randomized trial showed longer patency with covered SEMS [72]. A meta-analysis concluded that covered SEMS have a significantly longer patency compared with uncovered SEMS [73]. However, a subsequent meta-analysis found no difference in patency between covered and uncovered SEMS at 6 and 12 months, although covered stents had a higher rate of stent migration [74].

Another concern for patients undergoing placement of a covered SEMS who have an intact

gallbladder is the potential for developing cholecystitis due to obstruction of the cystic duct origin. Although the rate of developing cholecystitis as a complication after SEMS placement has been low in most studies, rates of up to 10 % have been reported [75, 76]. Some endoscopists routinely perform a biliary endoscopic sphincterotomy (B-ES) to facilitate SEMS placement and to help avert the risk of pancreatitis due to SEMS occlusion of the pancreatic duct. On the other hand, B-ES may itself be a risk factor for procedure-related complications including pancreatitis, bleeding, perforation, and stent migration. Studies comparing the outcome of SEMS placement in patients with and without a preceding B-ES have shown the following: (1) SEMS (covered and uncovered) may be placed without a B-ES with very high success rates equal to those who underwent B-ES prior to stent placement, (2) Avoiding a B-ES prior to SEMS placement may reduce the risk of complications, especially short-term complications such as bleeding and perforation [77, 78].

EUS-Guided Biliary Drainage

Despite a success rate of >90 % in most reports, ERCP with stent placement for malignant biliary obstruction occasionally fails owing to anatomical or technical problems. Surgically altered anatomy, gastric outlet obstruction, tumor infiltration of the ampulla, and periampullary diverticula may result in inability to reach or visualize the ampulla during ERCP. PTBD or surgical interventions are conventionally performed after unsuccessful ERCP. EUS-guided biliary drainage (EUS-BD) has recently emerged as an effective biliary drainage technique in cases of unsuccessful ERCP. Following the first report of EUS-BD by Giovannini et al. in 2001 [79], many groups have subsequently reported on the efficacy of EUS-BD as an alternative biliary drainage modality after unsuccessful ERCP [80–88]. EUS-BD is accomplished using one of three techniques. Transluminal biliary drainage involves accessing the common duct or a dilated left intrahepatic duct under EUS guidance, followed by dilation of the tract and placement of a stent between the common duct and duodenum (cholecystoduodenostomy) or the stomach and a left hepatic lobe duct (hepaticogastrostomy). The stent drains the biliary tree into the GI tract without crossing the site of biliary obstruction. In the EUS-BD rendezvous procedure, the biliary tree is accessed via the common duct or a left hepatic lobe duct and a guidewire is passed via the bile duct across the papilla into the duodenum. The EUS-placed duodenal guidewire is then used to perform ERCP in the usual retrograde fashion. It should be noted that the EUS guided rendezvous technique is possible only when the papilla can be reached endoscopically. With the EUS-guided antegrade technique, transgastric puncture of a dilated intrahepatic duct is performed followed by tract dilation and transpapillary placement a stent across the level of obstruction in antegrade fashion. The antegrade technique may be useful when the papilla cannot be reached endoscopically. EUS-BD is a technically complex procedure requiring advanced skills in interventional EUS. The overall success and complication rates are approximately 81 % and 15 %, respectively, in expert hands [47].

Efficacy of Preoperative Biliary Drainage

The benefit of PBD prior to pancreaticoduodenectomy in patients with resectable pancreatic cancer remains controversial despite numerous studies which have addressed this issue. Although several studies have suggested more perioperative complications in patients who underwent PBD, this approach remains popular in clinical practice. A recent study found that the use of preoperative biliary stenting doubled between 1992 and 2007, with most patients undergoing stent placement prior to surgical consultation [89]. Another study which evaluated the current clinical practice in pancreatic cancer surgery at German community and university hospitals found that of 102 returned questionnaires, 54 % preferred preoperative drainage procedures for cholestasis [90].

Several meta-analyses have evaluated the impact of PBD on the surgical outcome of patients with malignant obstructive jaundice undergoing pancreaticoduodenectomy [91–98] (Table 4.1). A 2002 meta-analysis by Sewnath et al. included 5 randomized control trials (RCTs) and 18 retrospective studies (RS) published from 1966 to 2001 [94]. They found that patients who underwent PBD had significantly higher overall complications (mainly PBD-related), prolonged hospital stays, and no difference in mortality compared to patients who went directly to surgery. This data led to the conclusion that PBD carries no benefit and should not be performed routinely. A second meta-analysis published in the same year which included two RCTs and eight RS concluded that preoperative biliary stent placement had neither a positive or adverse effect on surgical outcomes for patients with pancreatic cancer [93]. Velanovich et al. evaluated 1 RCT and 15 cohort studies, concluding that PBD increased postoperative wound infections by about 5 % but did not promote or protect from other complications [95]. Similarly, Garcea et al. found that PBD significantly increases the rates of bile culture positivity for bacteria and the probability of wound infection [91]. Otherwise, no evidence was found that PBD directly increases morbidity and mortality. Another meta-analysis in 2011 which reviewed 14 RS found no difference in overall postoperative complications or mortality between patients with or without PBD [92]. The authors concluded that PBD should not be used routinely for malignant obstructive jaundice. Fang et al. published a Cochrane review in 2012 which updated their previous meta-analysis from 2008 [96, 97]. Six RCTs were evaluated with 520 patients randomized (PBD-265, no PBD-255). They found no difference in mortality, but significantly higher serious morbidity in the PBD group vs. the direct surgery group. The study concluded that there is not sufficient evidence to support or refute routine PBD for patients with obstructive jaundice. Finally, a recent meta-analysis published in 2014

Table 4.1 Summary of meta-analyses evaluating the impact of PBD for biliary obstruction prior to pancreaticoduodenectomy

Author, year published	Types of studies evaluated	Conclusions
Sewnath, 2002	5 RCTs	– No benefit of PBD
	18 RS	– Increased complications due to PBD
		– PBD not recommended routinely
Saleh, 2002	2 RCTs	– No evidence that PBD has positive or negative effect on surgical outcome
	8 RS	
Velanovich, 2009	1 RCT	– PBD increased wound infections by 5 %. Otherwise, no impact
	15 RS	
Garcea, 2010	6 RCTs	– PBD caused bacterial contamination of bile and increased risk of wound infections
	30 RS	
Qiu, 2011	0 RCT	– PBD had no effect on overall morbidity or mortality
	14 RS	
Fang, 2012	6 RCT	– PBD increased risk of morbidity with no effect on mortality
	0 RS	– Evidence does not support or refute routine PBD
Sunm 2014	3 RCTs	– PBD not associated with increased overall morbidity or mortality
	11 RS	– PBD duration <4 weeks increases morbidity
		– Use of PBD selectively (>4 weeks drainage duration and use SEMS rather than plastic stents)

PBD preoperative biliary drainage, *RCTs* randomized controlled trials, *SEMS* self-expandable metal stents

reviewed 14 studies (3 RCTs, 11 RS) comparing PBD using endoscopic stents (plastic or metal) vs. no drainage [98]. The study found no difference in overall mortality or morbidity between the PBD group and the nondrainage group. Interestingly, a subset of the drainage group which had PBD for <4 weeks had an increased overall morbidity by 7–23 %; however, morbidity with PBD for >4 weeks was not significantly different. The authors concluded that PBD should be used selectively, drainage times should be >4 weeks, and SEMS should be used rather than plastic stents. Overall, the published meta-analyses have not definitively demonstrated benefits of PBD on the surgical outcomes of patients with malignant jaundice undergoing pancreaticoduodenectomy. It is important to note that the studies evaluated in various meta-analyses had significant variability in methodology, including older studies, making the data difficult to interpret in light of recent improvements in endoscopic and surgical techniques [11, 99].

The question of whether jaundiced patients with resectable pancreatic head cancer should undergo PBD or proceed directly to surgery was addressed by a recent large multicenter RCT involving community and academic hospitals [100]. Patients with obstructive jaundice and serum bilirubin levels ranging from 2.3 to 14.6 mg/dL were randomized to undergo either endoscopic placement of a plastic biliary stent followed by surgery 4–6 weeks later, or surgery alone within 1 week after diagnosis. The primary outcome was the rate of serious complications within 120 days after randomization. The reported rates of serious complications was 39 % in the early-surgery group vs. 74 % in the PBD group ($p < 0.001$). Although PBD was technically successful in 94 % after one or more attempts, the reported failure rate during the initial ERCP was 25 %. Of note, 46 % of patients in the PBD group experienced procedure-related complications such as pancreatitis (7 %), cholangitis (26 %), perforation (2 %), and bleeding (2 %). Surgery-related complications (e.g., infections, bleeding, anastomotic leaks) occurred in 37 % in the early surgery group and 47 % in the PBD group ($p = 0.14$). Mortality and length of hospital stay did not differ between the two groups. These results show that patients undergoing PBD have a higher overall complication rate, mainly as a consequence of the PBD procedure itself, and suggest that routine PBD should not be performed. As noted by Baron and Kozarek, the initial ERCP failure rate (25 %) and the procedural complication rate (46 %) reported in this RCT was much higher than reported in most studies for these outcomes (typically 5–10 % for both) [101]. The unexpectedly high rate of cholangitis (26 %) and need for stent exchanges (30 %) in the PBD group during the 4–6 weeks prior to planned surgery can likely be attributed to the use of plastic stents rather than SEMS in this study. As noted previously, multiple studies have shown that SEMS have a superior patency compared to plastic stents and can be used safely in patients who eventually undergo pancreaticoduodenectomy.

Summary and Conclusions

Although EUS with FNA is more sensitive than ERCP for tissue diagnosis of pancreatic cancer, many patients with obstructive jaundice continue to undergo ERCP as the initial procedure. A focal stricture seen in the bile duct and/or pancreatic duct during ERCP in a jaundiced patient should raise suspicion for malignancy and is an opportunity for tissue sampling via brush cytology, forceps biopsy, or both. Using a combination of sampling methods increases sensitivity.

The primary rationale of PBD is to reverse the adverse consequences of biliary obstruction on various organ systems (e.g., immune function, coagulation, renal, cardiovascular) with a goal of reducing complications after major hepatobiliary surgery. However, most clinical trials and numerous meta-analyses have not shown a clear benefit of PBD as a routine procedure for patients with resectable pancreatic cancer who are otherwise able to proceed directly to surgery. The most recent RCT found an alarming rate of PBD-related complications, suggesting that PBD should not be performed routinely [100].

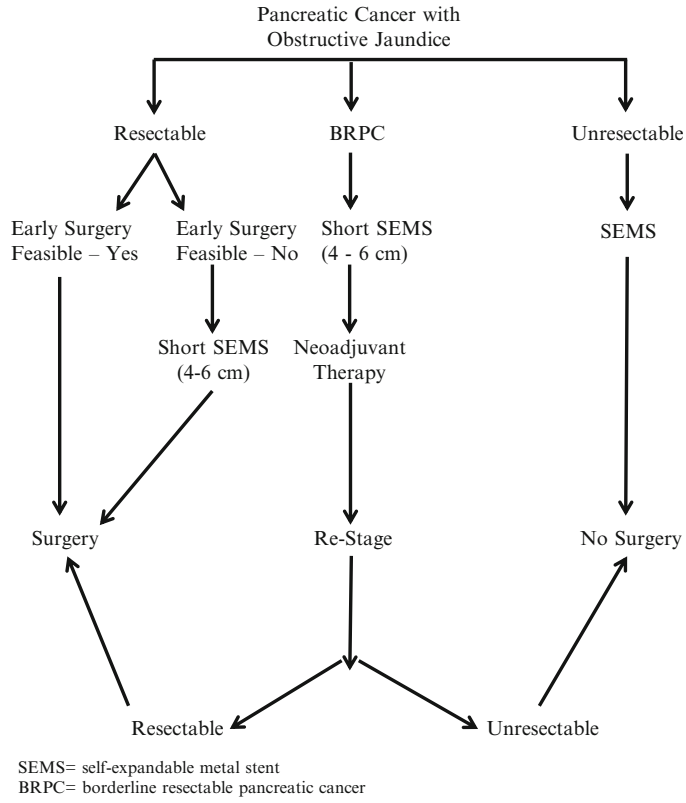

Fig. 4.11 Proposed algorithm for management of patients with obstructive jaundice due to pancreatic cancer

Improved technique and referral of patients to specialized centers with greater expertise could potentially lower the intrinsic risks of PBD.

Despite the controversy regarding its use, selected patients with obstructive jaundice due to resectable or borderline resectable pancreatic could still potentially benefit from PBD (Fig. 4.11). Although acute cholangitis is unusual in malignant obstructive jaundice in the absence of prior biliary intervention, patients who present with cholangitis should undergo urgent biliary decompression [43, 102]. Patients who have surgery delayed due to logistical reasons and those who require medical optimization or further staging should be considered for PBD. Finally, patients who undergo neoadjuvant chemoradiation therapy for borderline resectable pancreatic cancer or as part of treatment protocols may be candidates for PBD as a temporizing measure. In such cases, ERCP with insertion of a short SEMS is the preferred modality. Percutaneous biliary drainage procedures should be reserved for situations when endoscopic stent placement is unsuccessful. EUS-BD is also a feasible salvage technique for unsuccessful ERCP but is currently limited to centers with expertise in therapeutic endoscopy. Multidisciplinary treatment planning should be utilized whenever possible.

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Part 3

Multimodal Therapy

Overview of Multimodality Therapy

5

Robert de Wilton Marsh and Marshall S. Baker

Introduction

Pancreatic cancer is by nature biologically aggressive. Symptoms manifest late in the course of the disease, critical structures adjacent to the pancreas are often invaded or encased by tumor prior to diagnosis, and metastases occur early. There are, to date, no effective screening methods and few truly effective therapeutic options. As a result, this cancer continues to be one of the most challenging to treat and, although relatively rare by absolute incidence (46,420 cases in 2014—SEER), it has remained the fourth leading cause of cancer-related death in the USA for several decades.

There has been great effort in recent years to better understand the biology of this disease and to develop more effective treatment modalities. Practitioners in medical oncology, radiation oncology, surgery, and interventional radiology have stretched the limits of tolerable toxicity in an effort to help patients facing certain mortality. As a consequence, the number of therapeutic options has been substantially expanded and the potential morbidity of many of these treatments has increased. Patients and treating clinicians now have aggressive surgical, radiation and systemic therapeutic options to consider, particularly in the more localized forms of the disease. However, although most individuals will benefit to some degree from treatment, particularly in terms of progression-free survival, there is still a relatively low probability of definitive cure from any combination of available modalities. Given this scenario, the decision making involved in providing the best possible care for these patients has become much more complex, and the need for an appropriate multidisciplinary approach to care has become paramount. In this chapter, we discuss relevant advances in surgical oncology, radiology, pathology, radiation oncology, and medical oncology; we outline the key components of an effective multidisciplinary program and review the potential impact of multimodality care on patients with borderline resectable or locally advanced pancreatic cancer.

Classification

In 2009, a joint committee of the Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the

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Society for the Surgery of the Alimentary Tract (SSAT) published a consensus guideline on the classification of pancreatic cancer as resectable, borderline resectable, locally advanced unresectable, or metastatic [1]. The AHPBA/SSO/SSAT system is based on earlier work by the NCCN [2] and the group at the MD Anderson Cancer Center [3]. This system has been refined recently by the Intergroup and widely adopted nationally and internationally for use in the pretreatment classification of tumors [4, 5]. This has resulted in better, more reproducible selection of patients for appropriate therapy and for novel clinical studies. The system currently classifies a given tumor based on the presence or absence of identifiable metastatic disease and on the anatomic relationship between the tumor and the mesenteric and hepatic vasculature. It is now clear that resectability of a localized tumor, i.e., the expectation that a microscopically negative surgical margin (R0) can be safely achieved either prior to or after chemoradiotherapy, is critically dependent on the degree of arterial and venous involvement by the tumor at the time of diagnosis [6–8]. Almost any involvement of the portal and mesenteric vein is currently considered resectable, provided that portomesenteric continuity can technically be reestablished after an en bloc resection which includes the portal/superior mesenteric vein. For cases in which there is either celiac, hepatic, or superior mesenteric arterial involvement, the degree of vessel encasement is paramount. Abutment, and up to 180° encasement, is considered borderline resectable; more than 180° encasement is locally advanced and unresectable with the exception that, on occasion, isolated short segment encasement of the common hepatic artery may be resectable en bloc with reconstruction [5].

Recent publications using this system to classify patients offer some evidence that the borderline category, as defined by the AHPBA/SSO/SSAT system, does identify patients that stand to benefit from aggressive therapy. In a series of 47 borderline resectable patients analyzed by CT imaging following neoadjuvant therapy, partial regression in the degree of tumor/vessel contact was found to be a much better predictor of subsequent R0 resection than older measures such as change in size or attenuation of the tumor [9]. Twenty out of twenty-two patients with partial regression of tumor contact with any peripancreatic vascular structure (portal vein/superior mesenteric vein, celiac axis, superior mesenteric artery, hepatic artery) had an R0 resection. In contrast, reviews from both MD Anderson Cancer Center and Johns Hopkins University indicated that resection of borderline resectable pancreatic cancer after neoadjuvant therapy did not depend on improved radiographic appearance of tumor–vessel interface [10, 11]. In the first study, 122 patients had their disease restaged after receiving preoperative therapy, with the finding that 84 patients (69 %) had stable disease, 15 patients (12 %) had a partial response, and 23 patients (19 %) had progressive disease. Although only 1 patient (0.8 %) had their disease downstaged to resectable after receiving neoadjuvant therapy, 85 patients (66 %) were able to undergo pancreatectomy. In the second study, 58 % of borderline patients in their series underwent resection after preoperative therapy with a median survival of 22.9 months versus 13.0 months for those who did not undergo resection. Once again, tumor–vessel interface did not change significantly in either group.

Therapeutic Advances

Margin negative resection has traditionally been the only way to affect a cure in this disease. Although most patients with pancreatic cancer present with disease that is well outside the limits of what has heretofore been considered surgically resectable, in recent years there have been substantial advances in surgical methodology with newer techniques beginning to push the traditional physiologic and anatomic limits of resectable disease. Major advances include: minimally invasive approaches to resection of pancreatic cancer (addressed in Chap. 20) [12–14]; improvements in the techniques of portovenous, celiac, and hepatic artery resection and reconstruction (addressed in Chap. 20) [15, 16]; and more effective interventional methods allowing

better management of significant postoperative complications [17]. The enhanced ability to perform vascular reconstruction, in particular, has broadened the definition of what is considered anatomically resectable disease. This, in turn, has led to the recognition of a subset of locally advanced tumors that is neither clearly resectable nor unresectable based on the location and degree of vascular involvement by the tumor, and on other factors such as possible, but not definitive, radiologic evidence of metastatic disease and patient performance status [4]. It is estimated that as many as 16,000 cases of locally advanced disease are diagnosed each year, and that fully 5000 of these may be borderline resectable by current definitions. Resection in these cases may be technically possible but there is a perceived increase in the risk of significant postoperative morbidity and of surgically positive margins, and questions regarding the true benefit of an immediate surgical approach persist. True locally advanced disease is one step further from surgical intervention in that there is clearly greater than 180° encasement of one or more major arteries precluding any attempt at resection.

It is evident that even in cases judged de novo to be clearly amenable to a margin negative resection, surgery on its own is insufficient to affect a cure in the majority of patients, with both local and distant recurrence being the norm, and overall 5-year survival rates no better than 15–20 % in the best centers. While there will continue to be improvements in the surgical care of these patients, it is clear that improvements in surgical technique, alone, will never provide a definitive answer to this disease. Other modalities that have been used in effort to improve on results achieved by surgery alone include locoregional radiation and systemic chemotherapy. The addition of external beam radiation has been examined in a number of key studies, including a small randomized study performed in the 1980s by the GITSG (Gastrointestinal Tumor Study Group), in which encouraging results were obtained with fluorouracil (5-FU)-based split-course chemoradiotherapy—median overall survival of 20 versus 11 months [18]; a randomized study initiated some years later by the EORTC (European Organization for Research and Treatment of Cancer) which failed to confirm the benefit of radiation therapy [19]; LAP 07 which compared gemcitabine alone to gemcitabine followed by radiation therapy in locally advanced pancreatic cancer controlled by chemotherapy and which failed to show benefit with the addition of radiation therapy [20]; RTOG 97-04, which randomized patients to initial chemotherapy with either 5-FU or gemcitabine, followed by 5-FU-based chemoradiation to 50.4 Gy, followed by additional chemotherapy with 5-FU or gemcitabine, and which resulted in an improved rate of local recurrence in both arms of 25–30 % [21]; and a large multi-institutional retrospective pooled analysis which did show benefit to adjuvant chemoradiation after resection of disease with median O.S. of 39.9 versus 24.8 months [22].

The results of these aforementioned studies have been widely debated and, to date, a clear consensus on the overall efficacy of radiation has not been established. It is clear that when radiation is incorporated into the treatment plan: the quality of the radiation is critical; the rates of margin negative resection are improved; local recurrence is reduced, and some patients initially considered inoperable are converted into candidates for resection. The impact on overall survival, however, is not as clear. Furthermore, newer methods of administering radiation, such as intensity-modulated radiation therapy (IMRT) [23], stereotactic body radiation therapy (SBRT) [24], and even proton beam therapy [25], are engendering much excitement and may require a complete reexamination of how this modality is used.

Equally, chemotherapy historically did not play an important role in the management of localized pancreatic cancer. Significant progress in this regard was made with the discovery of the activity of single agent gemcitabine in 1996 [26], but it was not until newer regimens were developed such as gemcitabine, taxotere and capecitabine (GTX) [27]; 5FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) [28]; and gemcitabine plus nab-paclitaxel [29] that we began to think about the potential for meaningful

Table 5.1 Selected current studies in borderline resectable and locally advanced pancreatic cancer

Setting	Study	Regimen	Goal	Opened
Borderline resectable	ALLIANCE A021101 Pilot study	mFFX—no 5FU bolus—4 cycles, then RT/cape; gemcit postop	Accrual rate, toxicity, CR/PR, completion of all therapy, R0/R1	March 2013
Borderline resectable	Medical University of South Carolina Phase II	mFFX—no 5FU bolus—6 cycles then RT/cape	R0/R1 resection, (OS, TTR, ORR, path CR) and safety	August 2012
Borderline resectable	University of Maryland Pilot study	mFFX—no 5FU bolus—4 cycles then SBRT	Resectability, DFS, OS, TTR, path CR, and safety	September 2013
Locally advanced	UNC LINEBERGER Phase II	Standard full dose FFX	Assess safety and efficacy (OS, PFS, ORR)	September 2012
Locally advanced	Foundation for Liver Research/Erasmus Medical Center Phase II	Standard full dose FFX—4 cycles then SBRT	OS, radiologic RR, resection rate, PFS, biologic predictive markers	July 2014
Locally advanced	Massachusetts General Hospital/NCI Phase II	Standard full dose FFX—8 cycles plus losartan then proton beam RT	Feasibility, PFS, OS, toxicity, downstaging, gene mutations	March 2013

ORR overall response rate, *PFS* progression-free survival, *OS* overall survival, *CR* complete remission, *gemcit* gemcitabine, *SBRT* stereotactic body radiation therapy, *TTF* time to treatment failure, *cape* capecitabine, *TTR* time to response, *DLT* dose limiting toxicity, *DPD* dihydropyrimidine dehydrogenase, *MTD* maximum tolerated dose, *FFX* FOLFIRINOX

palliation and even cure. As can be seen from the prolongation of median survival in stage IV disease from a few months to almost a year with FOLFIRINOX, these newer regimens are considerably more active. It is hoped that this activity will translate into equally notable results in more localized disease; a selection of current studies incorporating these treatments in both borderline resectable and locally advanced pancreatic cancer is listed in Table 5.1.

In the last few years, there have been definite indications that supplementary therapy with more targeted agents, such as the EGFR inhibitor erlotinib [30], and genotype-directed choices such as PARP (poly(ADP-ribose) polymerase) inhibition with olaparib in BRCA-1 and 2 mutated individuals [31] could be the way of the future. The decision to use gemcitabine based on expression of the nucleoside transporter HENT-1 [32, 33] is also being investigated along with many other initiatives such as targeting the KRAS pathway [34] and the tumoral stroma [35], and these results are eagerly awaited. Finally, immunotherapy may shortly become yet one more therapeutic option [36]. Vaccines and immunomodulating agents are undergoing rigorous development and study and hold considerable promise, with a recent report of GVAX Pancreas Prime and Listeria Monocytogenes-Expressing Mesothelin (CRS-207) Boost Vaccines showing considerable prolongation of overall survival (9.7 versus 4.6 months) in patients with metastatic disease [37].

Imaging and Pathology

In parallel to the evolution in treatment of pancreatic cancer, there has been equally impressive progress in the imaging of this disease and in the ability to radiographically characterize the stage and biology of individual tumors. Understanding the technical developments in these areas underlines the importance of effective

multidisciplinary collaboration. Thin slice multi-detector CT imaging with oral and intravenous contrast, using non-contrast, arterial, pancreatic parenchymal, and portal venous phases, is critical to accurate assessment of the tumor and blood vessels. Anything less than the full pancreatic protocol sequences results in suboptimal imaging [38, 39]. If the patient has a contrast allergy, renal insufficiency, is pregnant or has inconclusive results on CT, then a pancreas protocol MRI may be used. MRI can be of particular value if small metastases to the liver or peritoneum are suspected [40]. Diffusion weighted MRI may even be of value in predicting response to neoadjuvant therapy [41]. Positron emission tomography (PET) scanning is increasingly being used to assist in planning for radiation therapy and to detect early metastatic disease not seen on routine imaging [42, 43]. It may also distinguish benign peripancreatic inflammation from metastases or local extension of malignancy [44].

Accurate staging is particularly germane in the management of patients with borderline resectable and locally advanced pancreatic cancer where agreement on definition is critical and standards of care are just now being developed to enable standardization of the therapeutic approach. The Society of Abdominal Radiology and the American Pancreatic Association have constructed a radiology reporting template which ensures that there is high quality and reproducibility to the reports, and this approach should rapidly be adopted by all institutions [45]. An abbreviated version of this template, as pertains to the critical vascular structures, is illustrated in Table 5.2.

Following surgery, the College of American Pathologists recommends a comprehensive and standardized analysis of each resected tumor which includes size, margins, histologic grade, nodal involvement, vascular involvement, lymphovascular invasion, perineural invasion, intraepithelial neoplasia, and any evidence of chronic pancreatitis [8]. This has permitted a more accurate assessment of the cancer prior to and following any therapeutic intervention and a more effective selection of appropriate local and systemic therapy. Handling of specimens, margin analysis, and the definition of an R1 resection still differs among pathologists in the USA and Europe. These variations need to be considered when analyzing study results [46]. An assessment of response to neoadjuvant therapy by the group at MDACC has determined that a full pathologic complete remission (2.7 %) or presence of minimal residual disease (16.1 %) following therapy has a much better prognosis than a moderate (55.6 %) or minimal response (25.6 %) and correlates with better survival [47].

Table 5.2 Abbreviated radiology checklist

Vascular involvement
[Include degrees (0–360) and length (mm/cm) of involvement or occlusion with image numbers]
1. Superior mesenteric artery (SMA): [no evidence of involvement/involvement]
2. Superior mesenteric vein (SMV): [no evidence of involvement/involvement]
3. Portal vein: [no evidence of involvement/involvement]
4. Celiac axis: [no evidence of involvement/involvement]
5. Hepatic arteries (common, proper, right, and left): [no evidence of involvement/involvement]
6. Gastroduodenal artery (GDA): [no evidence of involvement/involvement]
7. IVC and aorta: [no evidence of involvement/involvement]
Vascular anatomy
1. First jejunal branch of SMV: (anterior or posterior) to SMA
2. Variant anatomy

Endoscopy and Interventional Radiology

In the last 5 years, we have seen remarkable advances in endoscopic and interventional radiologic capabilities. Upper endoscopy, ERCP, and EUS have made a significant impact on the safety and accuracy of diagnosis and staging and on the management of common problems such as pain (celiac axis block) [48], biliary obstruction [49], duodenal obstruction, and postoperative complications. Duodenal obstruction has become an increasingly common problem in locally advanced disease as modern therapy has extended survival,

with one recent series reporting an incidence of 38 % [50]. Treating duodenal obstruction has become relatively routine, but managing the concomitant biliary obstruction when that occurs, frequently requires multidisciplinary experience. Creative endoluminal techniques such as double stenting and transmural biliary drainage techniques may be needed [51, 52].

Advances in interventional radiology have greatly contributed to improved management of symptoms related to disease and thus have allowed patients to initiate and complete neoadjuvant therapy. Percutaneous approaches to celiac neurolysis have improved the management of epigastric and back pain associated with celiac plexus infiltration [53], and percutaneous endovascular stenting has alleviated symptoms of intestinal and hepatic ischemia from tumor invasion into the SMA or hepatic arteries [8]. Percutaneous transhepatic portovenous stenting has been shown to be effective in the management of ascites resulting from portovenous tumor thrombus [54]. Finally, splenic artery embolization for non-operative management of low platelet counts as a result of hypersplenism has allowed continuation of dose-intensive chemotherapy in cases in which this has been important [55].

Key Components of the Multidisciplinary Approach

All these developments have created a menu of therapeutic and palliative treatment options that, individually, have uncertain potential benefit for any given patient. Each of the options in this menu has to be duly considered, with the risks and benefits carefully weighed. The optimal way to do so is to have every patient evaluated by individual experts from each of the disciplines involved, for there to be discussion among the members of that team, and a consensus approach to care developed.

Abundant evidence exists to support the notion that multimodality management of pancreatic cancer is associated with improved outcomes, with some centers demonstrating 5-year survival rates as high as 27 % among patients treated with multimodality therapy compared to 10–15 % in historical series with surgery alone [56]. There is also, however, considerable evidence that compliance with established national guidelines, such as that of the NCCN [8], remains disappointingly low [57], that there is considerable variability in the quality of the treatment of pancreatic cancer in the USA and that multimodality care is, as yet, still quite uncommon [58]. The optimal way to foster this multimodality care bears some scrutiny as different approaches may work better in different settings, and various disease specific groups may learn from one another. As the complexity of oncologic care continues to increase, it will be more important than ever that all involved in the care of the patient be experienced, knowledgeable, and current on new developments and that these experts communicate effectively.

The Multidisciplinary Conference

The cornerstone of quality multimodality care is most often the multidisciplinary conference (tumor board, cancer conference, HepatoPancreatoBiliary conference) which may meet on a weekly, biweekly, or monthly schedule. This gathering has been indispensable at well-developed cancer centers in regularly bringing all members of the care team together in a single forum in which each case can be reviewed and in which plans for treatment and research can be tailored to the specific needs of the patients and their pathology. The importance of multidisciplinary discussion is perhaps best exemplified by the finding, in a 2007 review of national practice from the national cancer database, that up to 40 % of patients with resectable peri-ampullary cancers were not offered surgery [59]. This finding was directly attributed by the authors to nihilistic bias on the part of certain members in the care team and would seem to reflect a lack of communication between treating and referring physicians.

The multidisciplinary conference as an entity has been studied. It has been established that the decision-making process promoted by these meetings reduces the variability engendered by

physicians acting independently [60], promotes enrollment on study protocols [61], and is essential for the integration of clinical information into quality biospecimen repositories [62]. It has been well documented that the conferences have a definite impact on the ultimate care plan, with multiple studies demonstrating that the ultimate recommendations for therapy are frequently changed (up to 43 % of cases) by the consensus opinion developed in the conference [63]. One recent prospective evaluation of practice patterns at a large tertiary cancer center found that 84 % of physicians were somewhat or very certain of their plans prior to conference and still changed their plans in 36 % of cases (72 % of those changes qualified as major changes) based on the conference's consensus recommendations [64]. The recognized importance of these meetings is underlined by the fact that both the Commission on Cancer and the American College of Surgeons require that institutions seeking accreditation have multidisciplinary conferences prospectively reviewing cases and discussing management decisions (Cancer Program Standards/American College of Surgeons). It is clear that institutional efforts to ensure accurate pathologic staging via synoptic analysis, to develop standardized templates for radiologic reporting, and to standardize protocols for therapy, promote cost-effective care that provides the best outcomes for the patients [56].

While there is a reasonably common format at larger institutions, it is worth reviewing the essential elements of an effective tumor board [61, 64, 65]. These elements are tabulated in a checklist format in Table 5.3. Meetings are increasingly organized by cancer type as treating physicians become more subspecialized. The conferences should ideally take place on a weekly schedule, thus enabling timely discussion and disposition of cases. While this frequency may not be feasible at all institutions, it promotes timely treatment planning and minimizes the time a patient waits for a decision regarding formulated algorithms. Appropriate physical space needs to be available on a regularly scheduled basis. This includes adequate seating for all participants, confidentiality (HIPPA), and availability of the necessary equipment for projection of radiologic images, endoscopic images, and microscope slides (and also videoconferencing if needed). Ideally, audiovisual/IT equipment may also permit the projection of computerized data such as treatment schemas, standards of care, investigational protocols, genomic and proteomic analysis, and collated data. Suggested participants should include all of the following: medical oncologists, surgical oncologists, radiation oncologists, gastroenterologists with endoscopic expertise, diagnostic and interventional radiologists, pathologists, geneticists, and a tumor registrar. We would argue that, under optimal conditions, having more than one individual from each discipline at the meeting affords more effective evaluation of the available treatment options. In reality, it is often difficult to consistently have more than one member of a given discipline at the conference. At a minimum, it is desirable to have multiple representatives from surgical oncology and medical oncology present. Additional members of the board may include oncology nurses, social workers, palliative care

Table 5.3 Comprehensive multidisciplinary conference checklist

	Y/N
Clearly designated leader	
Weekly schedule for timely discussion and disposition of all cases	
Appropriate physical space—adequate seating, confidential (HIPPA), quiet	
Appropriate equipment—projecting microscope, IT/visual equipment for projection of radiology and endoscopy images	
Audiovisual equipment for virtual meetings if needed	
Appropriate representation by all specialties: surgery, medical oncology, radiation oncology, interventional radiology, gastroenterology, radiology, pathology, primary care	
Additional desirable staff: nurses, social workers, nutritionists, pastoral care, geneticists, tumor registrar, and research associates	
Fellows, residents, and students where applicable	
Documentation of discussion and recommendations in secure, retrievable location	
Continuing Medical Education credits	
Method for communication of results to all stakeholders not present	

physicians and staff, nutritional services, pastoral care, and the patients' primary care physicians. Fellows, residents, medical students, and other trainees should attend and be encouraged to participate by case presentations and other means [66].

Attendance at these meetings by more marginal participants may be better when some form of incentive, such as continuing medical education (CME) credit, is provided. This is likely to be dependent on location and culture, and does not appear to be as important at academic centers (where many alternative sources of CME are available). One recent study of MDC conferences at a single academically affiliated tertiary center reported that only 24 % of attendees sought CME credits for their participation [67]. The time spent in such activity, in lieu of actual patient care, should be recognized by the institution, and participants should not be censured in any way. A clearly designated leader is essential to the smooth functioning of the conference [68, 69]. This individual should have the personal and professional respect of the members of the board, be knowledgeable and experienced, and be able to foster appropriate discussion. He/she should maintain decorum and ensure that differing opinions are rightly heard, that the meeting moves forward, and that it does not get bogged down over discussion of any one case. Finally, documentation of all cases presented in a concise, accessible format, along with diagnostic or therapeutic recommendations allows those not present to easily access this information. This facilitates the retrieval of data needed for analysis of conference utilization, tumor volumes, trends, and tissue banks.

Importantly, it should be noted that recommendations from a tumor board are recommendations and are not legally binding. These recommendations do not relieve the treating physician from the obligation to provide care for the patient. The treating physician must critically scrutinize the recommendations before implementation and, ideally, any deviation from these recommendations should be clearly explained based on the obligation to treat the patient safely and effectively [70].

Alternative and Complementary Arrangements

Several other elements of a multidisciplinary approach can be valuable adjuncts to the cancer conference but are not as commonly recognized and not as often employed across the country. A prime example is the multidisciplinary clinic [71]. For many reasons, this has not been as widely adopted as the multidisciplinary conference but may be of equal or greater value. Challenges to establishing this arrangement have included: limited clinical space to accommodate a larger group at one time; arranging appropriate support staff; scheduling of sequential patient visits; conflicting needs of surgical, oncologic, and medical specialties; entrenched attitudes to clinical care; and billing for services. Despite the logistic difficulties in establishing and maintaining these clinics, they have been consistently identified as enhancing the efficiency of care by allowing patients to see all of their care team in one visit. The clinics provide the opportunity for real-time interaction between members of the team who are treating diseases for which conditions change frequently. Including a specialist clinical cancer pharmacist in the clinic results in improved medication adherence ($p=0.007$) and patient satisfaction ($p<0.001$) [72].

In one notable study of the efficacy of a pancreatic cancer multidisciplinary clinic at Johns Hopkins Hospital, 25 % of patients had their care plan revised after analysis in the clinic, with both upstaging (29/38 patients) and downstaging (9/38 patients) of the original classification of the extent of disease [73]. Radiology review contributed the most to a change in plans (18.7 %) and pathology review was also important (3.4 %). One notable change in care was the determination of resectability in those cases where the portal vein/superior mesenteric vein confluence was involved. Patients identified in this study as having tumors involving the portal/SMV confluence had frequently been evaluated by programs at smaller referring hospitals, been deemed to have unresectable disease at these institutions and then were reclassified as resectable or borderline resectable in the multidisciplinary clinic.

Registration into the National Familial Pancreatic Cancer Tumor Registry was noted to increase from 49.2 to 77.8 % following initiation of this clinic, and participation in clinical studies was offered to 51/203 patients. The clinics also promote the academic mission, both by creating the appropriate environment to teach students, residents, and fellows in a multidisciplinary setting emblematic of modern oncology and by facilitating the determination of patient eligibility for clinical studies.

Virtual tumor boards, with secure access to protect patient confidentiality, are increasingly prevalent in regions where clinical volumes and practice patterns make a regular multidisciplinary conference practically impossible. This is particularly useful in a rural setting and where a large institution may have affiliates with which it wishes to coordinate care and clinical study accrual [74, 75]. This can also be helpful in complex diseases such as pancreatic cancer and in which access to tertiary care may be essential for multidisciplinary management and in which triaging patients for rapid referral may be critical [76]. In-person meetings where possible, however, still remain preferable as interactions are easier, the discussions are less regimented, and the number of cases presented is often greater [77].

Evolving experience with personalized care now suggests that a molecular or genomics tumor board may be a necessary addition to the more standard cancer conference discussed above, and many larger centers have such an entity. Most physicians do not have formal training in the evaluation of advanced genomics, and basic scientists, geneticists, and experts in bioinformatics may all contribute to the interpretation of results. In a recent series, 34 patients presented at a university molecular tumor board had a median of 4 molecular abnormalities each on next-generation sequencing, and no two patients had the same profile [78]. Eleven of 34 patients had treatment decisions informed by this test, and three of 11 had a meaningful response to treatment that was determined by molecular or genomic profiling. Barriers to therapy in those not treated were mainly related to access to appropriate agents. As the cost of genome sequencing declines, more and more patients with pancreatic cancer will have their cancers tested. Given the limited efficacy of current chemotherapy in pancreatic cancer, any leads engendered by this approach will be eagerly investigated.

Additional Participants and Resources

An often unsung member of the multimodality care team, not typically included in multidisciplinary conferences and clinics, is the primary care physician. Almost all patients with pancreatic cancer have concomitant medical conditions which require ongoing care and which are not optimally managed by physicians in specialty settings. These conditions may include diabetes mellitus, hypertension, malnutrition, cardiovascular disease, thrombosis and embolism, and intractable pain [79]. Further, the often long-standing relationship between patient and primary MD is a source of great comfort to many individuals, assuring them that they are following the right path in the treatment of their disease and providing essential moral support [80, 81]. Communication between the primary MD and the specialists is often not optimal but can and should be improved with better organization and structure [82]. Equally, all physicians are supported by nurses, technicians, dieticians, social workers, research associates, pharmacy staff, phlebotomists, and front office personnel. All of these individuals provide substantive psychosocial support for patients and technical skill sets without which their medical care would not be possible. These caregivers, and others, need to be rightly recognized as essential members of the cancer care team.

Finally, it is important to recognize the family and friends of the patient. These individuals are critical to the success of both the simplest and most complex treatment plan and without question impact clinical outcomes. Patients often rely on family members to provide transportation to treatment centers, fill prescriptions, administer medications, call insurance companies, report complications to treating physicians, and manage

households, in addition to offering emotional support and encouragement [83]. Because of the often terminal nature of this disease and the rapidity with which it may progress, there is frequently little time for caregivers to adjust to the circumstances facing their loved ones [84, 85]. These individuals may also be concerned about their own genetic risk and that of other family members [84]. It is becoming increasingly clear that although patients with well-developed support infrastructure and healthy caregivers cope better with the stress and the complexity of treatment than those who do not have such a system in place, the caregivers may themselves be at risk of illness and mortality [86]. As the disease progresses, these issues intensify and the quality of life of the caregivers may deteriorate significantly such that psychiatric care may be needed [87]. This is clearly a neglected aspect of comprehensive pancreatic cancer care, and future studies to examine more effective and meaningful interventions on their behalf are sorely needed. A recent pilot study to assess the experience of caregivers has demonstrated that these data are not only needed, but that the caregivers are very willing to share their stories and to seek assistance wherever they may find it [84].

Impact of Multimodality Care on Sequencing of Therapy

With the above infrastructure in place, a given case can be duly considered and the critical decisions necessary for optimal therapy can be made. As this decision-making takes place, a number of issues are critical. First, the goals of therapy must be clearly delineated—cure versus palliation versus other. It may not always be possible to do this, especially in borderline resectable disease where ultimate curability is uncertain, but a thorough understanding of the status quo on the part of the patient is essential if his/her expectations regarding the ultimate outcome are to be realistic. Second, the determination of eligibility for clinical studies is vital if important progress is to be made in this disease. It is estimated that only a very small fraction of all eligible patients are enrolled in clinical studies (3 %), with underserved populations rarely, if ever, exposed to available clinical studies and particularly prone to being neglected in this regard [88]. Third, individualized plans are ideally made with consideration given to stage of disease, tumor molecular profile, inheritance patterns, comorbidities, performance status, fragility scores, and cultural issues. Fourth, the skill set of the treating physicians and institutional experience must be considered. Many recent studies have demonstrated that outcomes of complex surgical procedures are better when the procedures are done in large centers performing a critical number of procedures on an annual basis [57]. When centers and physicians attempt procedures and therapies that they are not equipped or experienced enough to effectively carry forward, patients will not infrequently then need to be referred to tertiary centers where they may be offered second operations or attempts at treatment. Second procedures frequently do not have the desired results and an opportunity to cure may be lost [56]. Despite existing data supporting the importance of experience, there does not appear to be a migration to high-volume centers. There is a perception on the part of patients that remaining close to home is of definite benefit, and many procedures continue to happen in less experienced settings [57].

A typical patient will be referred with a mass on CT scan and/or obstructive jaundice, requiring a definitive diagnosis, relief of the jaundice (when present), and a complete staging evaluation. This will usually involve the assistance of a gastroenterologist or interventional radiologist. Once a biopsy has been performed and a tissue diagnosis confirmed, and biliary drainage has been established, a full staging evaluation can take place. This will usually consist of endoscopic ultrasound (EUS), CT imaging with pancreatic cancer-specific protocols, and perhaps MRI and/or PET scan. Together with a discussion of the patient's wishes, multidisciplinary review and an assessment of his/her performance status, an optimal plan can then be determined.

As noted previously, in the setting of borderline resectable, or locally advanced unresectable disease, it is now clear that a surgery-first

approach is unlikely to be the best option. There is a high likelihood of an R1 resection in the former, impossibility of complete resection in the latter, and significant delays in the initiation of adjuvant therapy or even no adjuvant therapy in up to 30 % of patients [58], particularly if there are surgical complications [89]. To this end, a neoadjuvant approach has been pioneered in recent years and initial results are promising. To date, only a handful of single institution studies or case series have been published [90–93]. The results of the Alliance A021101 study, the first multi-institutional prospective study in this setting, using four cycles of neoadjuvant FOLFIRINOX followed by RT/capecitabine, surgery, and then adjuvant gemcitabine for two cycles are eagerly awaited.

Optimal sequencing of available treatment modalities is still to be determined. An initial period of intensive chemotherapy, using one of the currently most active regimens such as FOLFIRINOX or gemcitabine/nab-paclitaxel, followed by combined radiation therapy and radiation sensitizing chemotherapy has become a popular and apparently effective choice [93–95]. The advantages of such an approach are not only the direct effect of the neoadjuvant therapy on the cancer, allowing effective surgery where this may not have been previously feasible, but also the early therapy of micrometastatic disease and the selection of patients with disease biologically appropriate for radiation and subsequently for resection. In published studies, this has allowed pathologic complete remission in fortunate individuals and successful R0 resection in a significant percentage of patients in both settings [93, 96, 97].

Postoperative treatment has often been recommended, but there is very little agreement on the optimal approach in this setting, and there has not been much in the way of innovation in this space. By default, many physicians have used single agent gemcitabine, which is the standard of care in resectable disease treated with immediate surgery, but results with this approach have been less than satisfying [98, 99]. This inclination to use gemcitabine may change with studies currently underway examining both more intensive chemotherapy and immunotherapy (PRODIGE 24/ACCORD 24 study) [100]. This is a particularly challenging issue as the performance status of patients who have completed a course of neoadjuvant treatment and then definitive surgery is often tenuous, and intensive treatment, while desirable, may not be tolerated. Nutritional status appears to be an issue in those patients who have received preoperative therapy and may delay the start of adjuvant therapy [101]. Fortunately, initial concerns that neoadjuvant radiation therapy or combined chemo/RT could result in an increase in major postoperative complications have not been validated [102–104]. A recent analysis of outcomes in the ESPAC-3 study determined that it was acceptable to wait up to 12 weeks after surgery before starting adjuvant therapy, providing that all six planned cycles were then given [99]. The number of treatment cycles rather than the time to start therapy appeared to be the more important parameter in this study. If this concept is validated in all adjuvant therapy, then this will allow patients to recover more fully from surgery before adjuvant therapy is started, thereby increasing their chances of completing the intended number of treatments.

A full complement of supportive medical care is a critical adjunct throughout treatment in this sequence. Paramount in all of these individuals is the need for adequate nutrition. An enteral feeding tube may have been placed at the time of surgery and up to 20 % of patients may need one later in the course of treatment [105]. Eating is a challenge in patients having had complex GI surgical procedures, and malabsorption of key nutrients is common owing to altered anatomy, delayed gastric emptying, and pancreatic insufficiency [106, 107]. This challenge needs to be addressed early and aggressively with a nutritional consult and follow-up, and with nutritional supplements and pancreatic enzymes as needed. Although enzyme use has been somewhat empirical to date, a new paper published in 2014 proposes a more rational approach to therapy with split administration of enzymes during a meal and with antacid and bicarbonate supplements to optimize the milieu [108]. Appetite stimulants

may also be tried although the efficacy of these is only fair at best, with megestrol and thalidomide seemingly the most effective to date but not without side effects [109, 110]. A stepwise approach to therapy, inclusive of anti-inflammatories, has been proposed and should be tested prospectively [111]. Even in patients surviving more than 6 months with apparently good nutrition, as assessed by body mass index, there can be significant micronutrient deficiency, especially iron, selenium, and Vitamins D and E [112].

Adequate pain control, psychological and social support, and physical therapy and rehabilitation as needed complete the menu of supportive care modalities. Global quality of life in most domains appears to return around 6 months after surgery on average [113]. Employing an exercise regimen during and after adjuvant therapy appears to hold promise for improved function and recovery [114, 115]. Follow-up is typically every 3 months in the first 2 years and then every 6 months for years 3–5 as per NCCN guidelines. This includes history and physical examination, lab tests including a CA 19-9, and CT imaging. It is unclear whether this program impacts on patient survival or quality of life, but with evolving options for treatment of recurrent disease it would seem to be prudent to follow these recommendations.

Conclusion

In summary, multimodality therapy of borderline and locally advanced pancreatic cancer has become the norm in most larger and experienced centers. Multidisciplinary evaluation and discussion has the potential to profoundly impact care of the patient, from the inception of treatment through long-term surveillance and follow-up. The essential elements of a comprehensive multidisciplinary program have been explored and proposed, and the need for standardization in diagnosis, classification, reporting, and therapy has been emphasized. Subsequent chapters will explore many of these issues in depth.

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Role of Systemic Therapy

6

Matthew J. Reilley and Gauri R. Varadhachary

Introduction

Management of resectable and borderline resectable pancreatic adenocarcinoma (BRPC) represents a significant challenge. Unfortunately, in most patients, PDAC is a systemic disease at presentation. Even in the presence of excellent perioperative supportive care and low mortality in high-volume centers, approximately 80 % of patients who undergo resection will develop metastases and die of their disease within 5 years [1, 2]. This is because most patients likely have micrometastatic disease at the time of attempted curative resection [3].

In the era of the multidetector CT optimized for pancreatic imaging, tumors of "borderline resectability" have emerged as a distinct subset of PDAC. The attempt to standardize the definition of borderline resectable is work in progress. As discussed elsewhere, the criteria has been modified with time through the National Comprehensive Cancer Network (NCCN), initial descriptions from M. D. Anderson Cancer Center (MDACC), and consensus conferences, the first being sponsored by the AHPBA/SSAT/SSO. Patients with BRPC are poor candidates for upfront surgery because they are at a high risk for margin positive resection with initial surgery. Multiple studies have reported that patients with margin positive resection do poorly with a life expectancy between 8 and 12 months, which is no different from patients with locally advanced pancreatic cancer [4, 5]. The rationale for pursuing preoperative treatment for a patient with BRPC is similar to patients with potentially resectable pancreatic cancer although with a greater emphasis on maximizing R0 resection. Additional justification for preoperative therapy includes treating micro metastatic disease early, giving majority of the "adjuvant" therapy in a "neoadjuvant" setting when it is better tolerated. Using this approach to gauge the aggressiveness of the cancer selects patients for surgery who have the greatest likelihood of a favorable postoperative outcome especially given the morbid nature of the surgery. Data also suggests that preoperative chemoradiation may decrease the incidence of pancreaticojejunal anastomotic fistula, a common complication following pancreaticoduodenectomy or distal pancreatectomy. Therefore, although the sequencing and duration of preoperative treatment modalities remain elusive, most agree that a treatment schema that incorporates

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systemic chemotherapy and chemoradiation is the optimal strategy for BRPC and this notion has been embraced by several institutions and high-volume pancreatic cancer centers.

Herein, we describe the current status of preoperative systemic chemotherapy approach to BRPC. There is considerable controversy on the topic, including rationale, best regimens, duration of therapy, standardization of surgical techniques, selection of patients for chemotherapy, chemoradiation versus both, and sequencing of these approaches. Analyzing retrospective, single-institution and small prospective studies makes it a challenge and emphasizes the importance of multi-institutional prospective clinical studies in this setting.

Adjuvant Trial Results Inform Preoperative Approach

While treatment with a fluorouracil-based (5-FU) regimen for unresectable pancreatic cancer became standard in the 1980s, there were limited trials investigating the role of adjuvant chemotherapy [6]. The earliest randomized prospective trial was published in 1985 by the Gastrointestinal Tumor Study Group (GITSG) [7]. The study enrolled 43 patients randomized to observation or 5-FU based chemotherapy with radiation after surgery. They found a significant benefit in overall survival at 20 months in the treatment arm versus 11 months in the observation arm. However, the small size of the study combined with poor baseline overall survival limited broad acceptance of these findings.

Follow-up investigations explored role of adjuvant chemotherapy, chemoradiation, or a combination. The European Organization of Research and Treatment of Cancer (EORTC) organized a study comparing 5-FU based chemoradiation versus observation in patients with resected pancreatic head or periampullary cancers. Pancreatic head adenocarcinoma patients in the treatment group derived an average improvement in overall survival of approximately 4.5 months, unfortunately the study was under powered for this subgroup ($p=0.099$) [8]. A more recent adjuvant trial from the European Study Group for Pancreatic Cancer (ESPAC) compared observation to chemotherapy with 5-FU daily for 5 days each month for 6 months, chemoradiation with 5-FU and 20 Gy, or combination [9]. The results of ESPAC-1 demonstrate an improvement in overall survival among those treated with chemotherapy, with median survival of 19.7 months compared with 14.0 months in those who had not received chemotherapy [10]. The investigators reported that the use of chemoradiation did not improve survival and indeed may have a confounding negative effect when combined with chemotherapy.

The CONKO-001 trial compared adjuvant treatment with gemcitabine for 6 months with observation following surgical resection and found evidence of both disease-free and overall survival with adjuvant chemotherapy [11]. Recently published long-term outcomes data solidifies the benefit to gemcitabine in the adjuvant setting. The treatment group had significant improvement in disease-free survival at 13.4 months versus 6.7, and a near-doubling of 5-year survival rates [12].

Current trials of adjuvant therapy have clearly demonstrated a small but absolute benefit of systemic therapy for the prevention of disease recurrence. The assumption is that this benefit derives from treatment of microscopic disease that is neither clinically or radiographically apparent. The ESPAC and CONKO results have helped to establish 5-FU and gemcitabine-based chemotherapy regimens as effective in pancreatic adenocarcinoma. These trials inform the neoadjuvant space and help solidify the rationale for using systemic therapy in the neoadjuvant setting.

Preoperatively, combination therapy is more standard than in the metastatic setting. As with earlier single-agent studies, ongoing multiple agent chemotherapy trials in advanced disease will offer insights applicable to neoadjuvant treatment. The ongoing APACT study with nab-paclitaxel and gemcitabine versus gemcitabine alone (NCT01964430) seeks to answer the combination question in the adjuvant setting—the outcomes will provide insights relevant to neoadjuvant therapy. Ultimately, the results of these adjuvant trials are instructive in the treatment of borderline resectable disease as the goal

of chemotherapy in both settings is to reduce postoperative disease recurrence. Incorporating novel agents in the adjuvant setting will further inform the preoperative platform. The role of adjuvant chemotherapy in BRPC remains unclear; however, the outcomes of trials such as APACT may inform future areas of investigation.

Retrospective Studies with Preoperative Chemotherapy in BRPC

Given the sound biologic and clinical rationale for the preoperative approach to operable PDC [13–15], it is not surprising to see an evolving acceptance of this method for BRPC. The first trials for preoperative therapy of BRPC were planned approximately a quarter of a century ago. A small trial published in 1990 treated patients with locally advanced pancreatic adenocarcinoma with para-aortic adenopathy with neoadjuvant chemoradiation prior to surgical exploration [16]. Patients received infusional 5-FU, bolus mitomycin-C, and radiation therapy for 3 weeks of treatment prior to CT restaging. Over 80 % underwent surgical exploration after completing therapy and approximately 75 % of those patients had their malignancy resected. Two-thirds of the patients who were resected were alive at time of publication; however, the follow-up time frame for most patients was less than a year. Additionally, the small study size and lack of anatomic details limit generalizability to the borderline resectable population. Regardless, this prospective trial gave early suggestion that neoadjuvant therapy may improve survival in patients with initially non-resectable disease.

In 1997, Lu and colleagues conducted a prospective analysis of the utility of a preoperative CT scan in predicting resectability based on degree of vascular involvement [17]. Specifically, they designed a grading system characterized tumor involvement of the portal and superior mesenteric veins (PV/SMV), and celiac, hepatic, and superior mesenteric arteries based on circumferential contiguity of tumor to vessel. Tumor involvement of 80 vessels was analyzed, and they found when using a threshold of 180° unresectability could be predicted with very high specificity and high sensitivity. More recent studies that utilize multimodal therapy, including neoadjuvant treatment, have demonstrated the 180° threshold is highly specific for identifying unresectable disease [18–20].

The concept of borderline resectable disease was first established in the literature in 2001 with the term "marginally resectable" which was applied to cancer involving the portal vein, superior mesenteric vein, or superior mesenteric artery (SMA) [21]. Since, the definition of borderline resectable pancreatic cancer has evolved to include involvement of the celiac axis, common hepatic artery (CHA), and SMA, and PV/SMV [22]. Extent and characteristics of vascular involvement remain controversial and are discussed in greater detail in other chapters. Accurate imaging with pancreatic-phase thin-section helical CT plays an essential role in determining borderline resectable status.

Recognizing that borderline patients represent a unique disease phenotype, there have been several efforts to retrospectively identify BRPC cases. Table 6.1 outlines key characteristics of several recent and sizable retrospective studies. It is important to note that the criteria used to identify patients as borderline resectable are not uniform between these studies. Additionally, some include non-borderline cases, but the table reflects only the data from BRPC patients.

MDACC published one of the largest retrospective studies to date [23]. 129 patients were identified as borderline resectable by either MDACC or AHPBA/SSO/SSAT criteria; 70 met both sets of criteria. Patients were primarily treated with either sequential gemcitabine-based chemotherapy followed by chemoradiation or chemoradiation alone. A majority of patients underwent resection and nearly all achieved R0 resection. The average survival in the surgical group was 32 months while in the unresected population it was only 12 months. Benefit was seen even though preoperative therapy rarely resulted in clinically relevant downstaging of tumors. Importantly, this study shows benefit from chemoradiation independently or in sequence with chemotherapy.

Table 6.1 Retrospective trials with neoadjuvant chemotherapy in BRPC

Reference	BRPC cases	Regiment	Number resected (%)	R0 resection (%)	OS, all pts (mo)	OS, resected pts (mo)
Turrini [85]	49	5-FU/Cis + XRT	9	[b]	[b]	[b]
Chun [24]	74	5-FU/Gem + XRT	74	44 (59 %)	[b]	23
Stokes [25]	40	Cape + XRT; Adj GEM	16 (46 %)	12 (75 %)	12	23
Barugola [86]	27	GEM +/− Cape/OX; then XRT + GEM +/− Cis/Cape	41	29 (71 %)	27.8	35
Katz [23]	129	GEM +/− Cis; GEM/5-FU + SBRT	85	81	22	32
Kang [87]	35	GEM +/− Cis + XRT	32	28	26.3	32.6
Chuong [26]	57	GTX; then SBRT	32 (56 %)	31 (97 %)	16.4	19.3
Kharofa [88]	39	Multiple	22 (56 %)	22	20.4	26.4
Paniccia [31]	20	FOLFIRINOX	17 (85 %)	17 (100 %)	[b]	[b]
Blazer [32]	18	mFOLFIRINOX	11	9	21.2	[a]

[a]OS endpoint not reached

[b]Not provided

Chun et al. [24] looked specifically at the impact of neoadjuvant chemoradiation on margin negative resection in borderline resectable cases involving the portal or superior mesenteric vein (PV/SMV). They compared 74 preoperatively treated patients to 35 that received upfront surgery. Of those treated, 78 % received gemcitabine-based chemoradiation while 22 % received 5-FU based chemoradiation. They found improved survival with chemoradiation in patients with unilateral involvement of the PV/SMV (Ishikawa type II and III); however, there was not a significant survival benefit with bilateral involvement (Ishikawa type IV and V). Overall, preoperative therapy and margin negative resection status both were associated with improved survival in these cases involving the PV/SMV.

Stokes and colleagues [25] evaluated patients with borderline resectable disease by the MDACC classification who were treated with preoperative capecitabine with radiation. Among the 40 BRPC patients, 85 % completed therapy and 16 underwent resection. R0 resection was achieved in 75 % of surgical cases. The authors conclude that capecitabine-based chemoradiation is well tolerated and effective in selecting patients most likely to benefit from surgery.

A single-institution analysis out of Moffitt [26] looked at sequential induction with 3 cycles of chemotherapy followed by SBRT in a cohort of BRPC patients. 66 % of patients received a combination of gemcitabine, docetaxel, and capecitabine (GTX) and the majority received gemcitabine-based therapy. Of those treated, 56 % went to surgery and 97 % of those achieved an R0 resection. Among these, three patients had a pathologic complete response (pCR) and one had a near pCR. These four patients were all treated with GTX and none had relapsed at time of publication. This result offers a suggestion that multi-agent chemotherapy regimens such as GTX may more effectively control micrometastatic disease than single-agent chemotherapy regimens.

An approach combining 5-FU, leucovorin, irinotecan, and oxaliplatin, collectively referred to as FOLFIRINOX, is an important treatment regimen that has become more common in the past several years. This regimen was developed for metastatic disease given from evidence that 5-FU plus oxaliplatin [27] and irinotecan [28] independently are effective in metastatic pancreatic adenocarcinoma. The regimen was reasonably tolerated with overall improvement in quality of life [29]. Subsequently, in a large phase III trial comparing FOLFIRINOX to gemcitabine, FOLFIRINOX was found to be superior in both progression-free and overall survival [30].

Of critical importance, FOLFIRINOX demonstrated a highly significant improvement in response rate, 31.6 % versus 9.4 % in the gemcitabine group. As a result, there is a strong desire to test the role of this regimen in the neoadjuvant setting.

Several small trials have reported positive outcomes with FOLFIRINOX in the preoperative setting. Paniccia [31] reported on a small retrospective cohort of patients who received FOLFIRINOX. Approximately half received only chemotherapy while the rest received chemotherapy followed by chemoradiation. In spite of expected toxicities, nearly 90 % of patients completed chemotherapy. 85 % underwent resection and all those patients achieved R0 resection. A separate study looking at a modified FOLFIRINOX regimen with reduced doses found similar rates of resection and high R0 resection rates with less toxicities [32].

While these retrospective studies yield valuable information, they have several limitations. Many early reviews have limit numbers of borderline cases or conversely do not explicitly define the criteria used to define patients as borderline resectable. Fortunately, more recent studies tend to have crisper definitions that make the resultant findings more application to this population. A major challenge is that most studies mix neoadjuvant treatment regimens. As such, it is difficult to determine what components of chemotherapy or chemoradiation are providing the most benefit. Fortunately, there are several small prospective trials to evaluate neoadjuvant regimens and several ongoing larger randomized controlled trials that are improving our preoperative chemotherapy regimens.

Prospective Studies with Preoperative Chemotherapy in BRPC, including Current Trials in Progress

Retrospective studies of borderline resectable disease provide a strong suggestion that patients benefit from presurgical chemotherapy. A variety of prospective trials with a borderline population have been conducted in the past decade to identify the most effective regimens and many trials are ongoing. First, we will highlight several prospective studies investigating the role of neoadjuvant chemotherapy as single-modality therapy in patients with BRPC.

Sahora et al. published the results of two separate phase II studies with neoadjuvant gemcitabine plus either oxaliplatin or docetaxel. In the gemcitabine and oxaliplatin (GemOx) study [33], patients received 6–9 weekly doses of GemOx with restaging and surgical exploration if evidence of response on imaging or clinically. Of the 15 patients who were classified as borderline resectable at enrollment, 47 % underwent surgical exploration. R0 resection rate was 69 %, and median survival was 22 months for resected versus 12 months for unresected patients. The gemcitabine and docetaxel (GemTax) trial [34] treated patients with 8 weeks (2 cycles) of GemTax prior to restaging. Patients with partial response or stable disease with improved clinical condition were taken for surgical exploration. Of the 12 patients with BRPC at study entry, 7 (58 %) underwent surgical exploration and ultimately 4 (33 %) were resected with curative intent. The overall R0 resection rate was 87 %. Median survival among resected versus unresected patients was 16.3 months versus 12.2 months, respectively.

A separate phase II study examined the role of neoadjuvant dose-dense gemcitabine and capecitabine (GX) in locally advanced pancreatic cancer [35]. Treatment typically consisted of 2 weeks of weekly gemcitabine and daily capecitabine on a 3-week cycle. Average number of treatment cycles was three. Per protocol, patients were classified as borderline resectable based on NCCN criteria and 18 BRPC patients were enrolled along with 23 unresectable patients. A total of 11 (61 %) underwent surgical resection and 9 of 11 (82 %) were R0 resections. Interestingly, the authors also analyzed patients based on Asian Pancreatobiliary Cancer Center (APBCC) criteria which results in 33 out of 43 patients being classified as borderline resectable. With broader inclusion criteria, a smaller proportion of patients (46 %) underwent resection, yet a greater number, 13 of 15 (87 %) were R0 resections. The median survival of resected patients was 23.1 months com-

pared with 13.4 months in unresected patients. This trial also demonstrates the importance of standardization of BRPC criteria. The internal variability of results based on the borderline resectable classification system demonstrates the challenge of comparing results between trials.

Most centers use a combination of chemotherapy and chemoradiation therapy for neoadjuvant treatment of pancreatic adenocarcinoma, and many trials combine these modalities of treatment. Chemoradiation therapy can be delivered independently or sequentially with chemotherapy to treat BRPC. There is evidence supporting the use of 5-fluorouracil agents (infusional 5-FU or capecitabine) [36, 37] or gemcitabine [38, 39] as radiosensitizing agents in combination with radiotherapy. The NCCN notes that no standard chemoradiation regimen exists for the treatment of borderline resectable disease. Other chapters of this textbook will discuss the data supporting chemoradiation in greater detail.

Mehta and colleagues conducted the earliest prospective trials of preoperative chemoradiation in patients with borderline resectable characteristics. Specifically, they enrolled patients with pancreatic adenocarcinoma had greater than 1 cm of tumor abutment, but less than 180° involvement of the PV, SMV, or SMA [21]. Patients received protracted 5-FU infusion with concurrent radiation totaling between 50.4 and 56 Gy. Of those treated, 60 % underwent R0 resection and had a median survival of 30 months compared with 8 months for the remaining unresected patients.

A recent study by Takahashi et al. investigated a regimen of gemcitabine-based chemoradiation followed by gemcitabine in resectable and borderline resectable patients [40]. Of 80 BRPC patients, resection rate was 54 %, and among those resected 34 % were alive at 5 years. Notably, distant and peritoneal recurrence was significantly higher in the BRPC group than the baseline resectable cohort. In this study, neoadjuvant gemcitabine-based chemoradiation seems to be an effective therapy for resectable or BRPC. Given higher rates of recurrence, borderline resectable patients may benefit from higher intensity chemotherapy regimens in the neoadjuvant setting. Further trials investigating role of chemoradiation therapy are ongoing.

Subsequently, a large number of trials to evaluate the efficacy of neoadjuvant or preoperative chemotherapy in borderline or unresectable tumors have been conducted. A recent meta-analysis identified 57 studies that examined preoperative treatment with chemotherapy, radiation therapy, or chemoradiation in patients with unresectable tumors at diagnosis [41]. In their analysis—of patients with initially unresectable disease treated with neoadjuvant therapy—4.8 % achieved a complete response and 30.2 % achieved a partial response. These rates were higher with combination chemotherapy compared with monotherapy. Significantly, 33.2 % of patients underwent surgical exploration with resection; of these, 79.2 % of patients achieved an R0 resection. The profound implication of this meta-analysis is that preoperative therapy, with an emphasis on systemic therapy, offers the opportunity for a subset of patients previously considered incurable to be treated with curative intent. Importantly, the meta-analysis did not find a significant difference in the outcomes of patients initially presenting with resectable disease receiving neoadjuvant therapy compared with adjuvant. This highlights the importance of having criteria to identify which patients are unresectable and most likely to achieve R0 resection with neoadjuvant treatment.

There are multiple ongoing investigations into systemic neoadjuvant treatment options for BRPC. In addition to trying to find an optimal response rate, there is interest in achieving a balance of efficacy and toxicity. As many of these studies are in progress, it is premature to widely generalize results to broader patient populations; however, there are exciting signals for novel combinations and/or therapeutics.

Several early phase trials are investigating role of S-1, alone or in combination, for the treatment of BRPC. S-1 is an oral medication that consists of tegafur, a prodrug of 5-FU; gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor; and oteracil, an inhibitor of phosphorylation in the gastrointestinal tract. The prodrug is converted into active 5-FU via hepatic metabolism and degradation is blocked by inhibition of DPD. Two phase III studies conducted in Japan demonstrated non-inferiority to gemcitabine in

the unresectable setting [42], and superiority alone or in combination with gemcitabine in the adjuvant setting [43, 44]. In one phase II trial, 35 BRPC patients were treated with combination gemcitabine and S-1. 27 had no evidence of distance metastatic disease at time of resection and had a median survival of 34.7 months compared with 10.0 months for those with unresectable or metastatic disease [45]. Another trial of chemoradiation therapy with S-1 enrolled 28 patients, 25 of whom completed treatment. 24 (85.7 %) underwent surgical resection and all achieved R0 resection. All resected pathology specimens had Evans' grade IIa response, and 14 had grade IIb or greater reduction in tumor cells [46]. The large phase III trials of S-1 have taken place in Japan and there are concerns about how the toxicity profile, particularly in Western populations, may limit utilization of this drug [47]. These results are encouraging and trials of S-1 compared with the more aggressive and established neoadjuvant regimens are necessary.

Gemcitabine and nab-paclitaxel is an effective treatment for pancreatic adenocarcinoma in the metastatic setting. An early phase study of this combination demonstrated good tolerability and a promising response rate in the metastatic setting [48]. The IMPACT trial compared this regimen to gemcitabine alone and found a good improvement in response rate of 23 % versus 7 % in the experimental and control arms, respectively [49]. There are case reports describing the use of this regimen in the locally advanced setting with good response leading to resection [50]. Figure 6.1 demonstrates tumor and Ca 19-9 response in a patient treated with gemcitabine and nab-paclitaxel. Current ongoing trials are comparing these agents to FOLFIRINOX, in

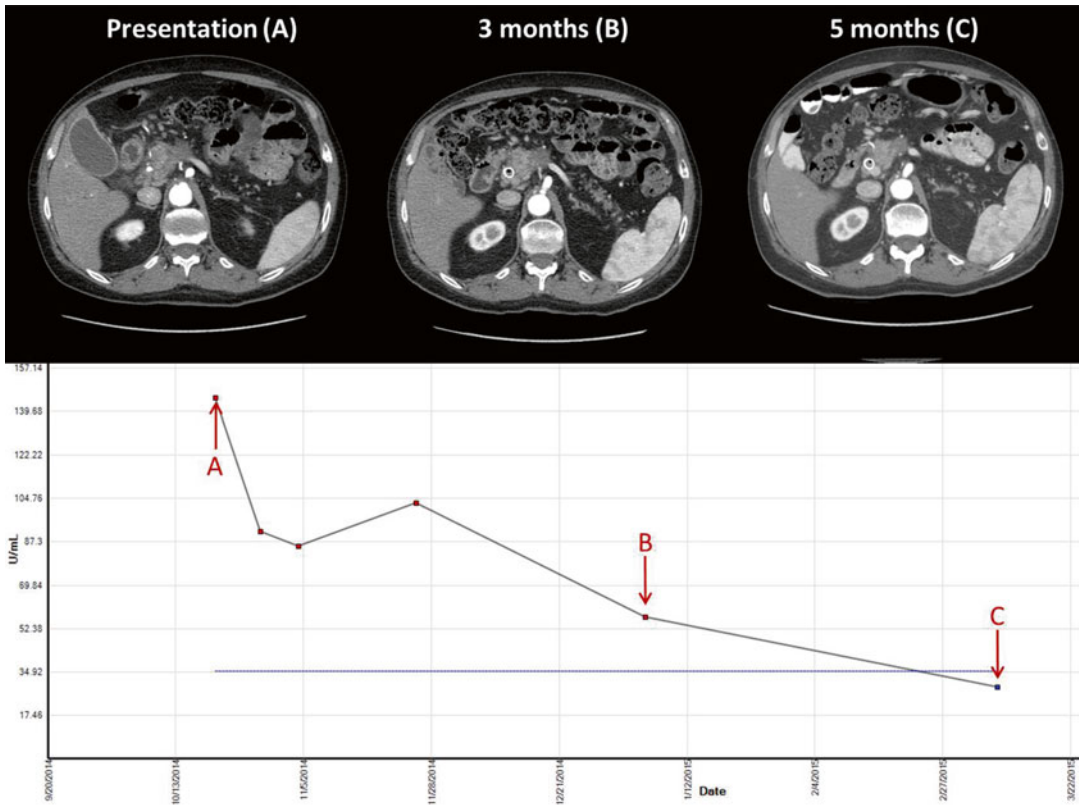

Fig. 6.1 Imaging and Ca 19-9 levels in a 67-year-old male patient with borderline resectable pancreatic adenocarcinoma treated with gemcitabine and nab-paclitaxel for 5 months followed by capecitabine-based chemoradiation therapy receiving a total of 50.4 Gy

combination with radiation therapy, or even with novel targeted agents. Evidence-based data on the utility of this regimen in the borderline resectable population is under active investigation.

FOLFIRINOX is being actively trialed in the BRPC population. Retrospective studies discussed earlier have shown much promise; however, validation from prospective trials is forthcoming. The Alliance A021101 intergroup trial for BRPC is a large trial to evaluate preoperative FOLFIRINOX followed by capecitabine-based chemoradiation and is currently ongoing. As an example, Fig. 6.2 demonstrates response to treatment without evidence of recurrence in a patient treated with FOLFIRINOX. Reduced intensity FOLFIRINOX is appealing as it seeks to combine the benefit of triple-agent therapy while minimizing dose-related toxicities. Retrospective studies have shown similar benefits to full dose therapy with fewer side effects [32]. However, prospective trials are needed. Several smaller prospective trials are investigating FOLFIRINOX in the resectable or locally advanced setting. A phase 2 trial at MDACC is investigating modified preoperative FOLFIRINOX and chemoradiation in high-risk resectable and borderline resectable pancreatic cancer patients. To date, using strict inclusion criteria for high-risk disease resection rates are approximately 50 %. While the data is still evolving, approximately 40 % of resected patients have demonstrated early recurrence at less than 1 year postoperatively. Importantly, it appears that aggressive therapy does not rescue aggressive biology in these patients. Therefore, better methods to identify the patients most likely to benefit from therapy are needed. NCT-01992705 is specifically investigating BRPC and combines this chemotherapy with SBRT; a similar trial, NCT-01897454, combines chemotherapy with gemcitabine-based radiation therapy. There is

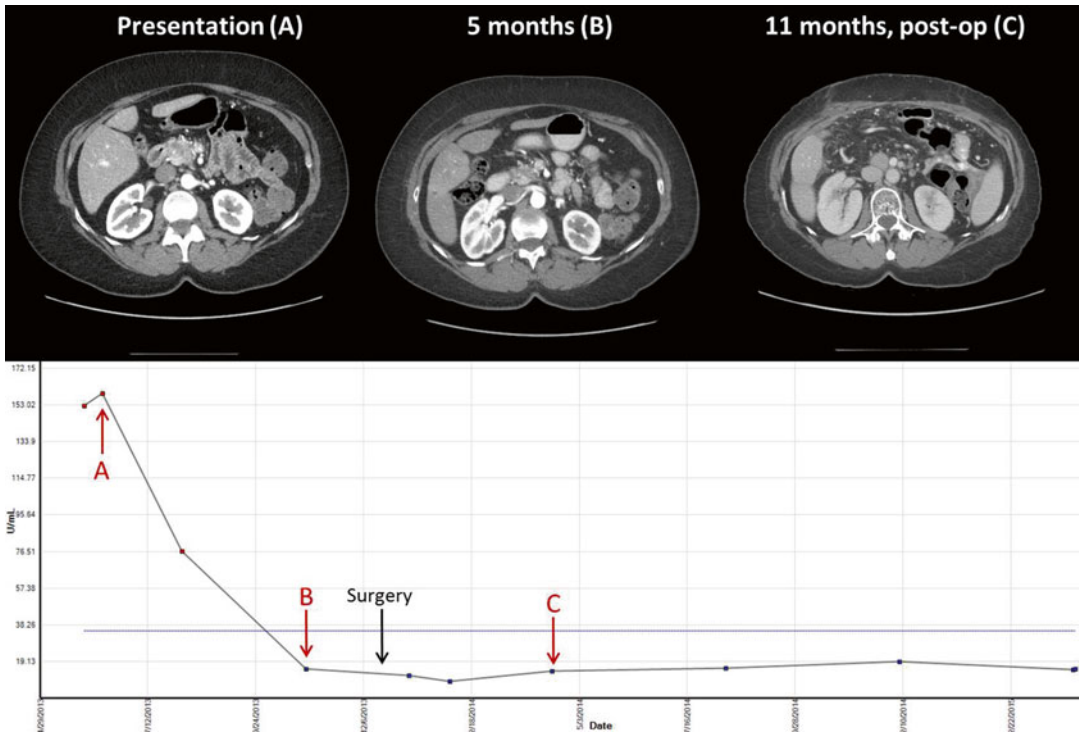

Fig. 6.2 Imaging and Ca 19-9 levels in a 51-year-old female with borderline resectable pancreatic adenocarcinoma treated with FOLFIRINOX for 2 months with dose reduction of oxaliplatin. This was followed by capecitabine-based chemoradiation with 50.4 Gy. CT images and Ca 19-9 levels include before and after surgical resection of primary tumor

interest in combining immunotherapy modalities to target the immunosuppressive environment in pancreatic adenocarcinoma. NCT-01413022 is a phase Ib study combining FOLFIRINOX with a novel CCR2 inhibitor, an agent that has been shown to target infiltrating, inflammatory macrophages [51], demonstrated promising early results [52]. The results of multiple ongoing preoperative trials of FOLFIRINOX and other novel agents will provide a better understanding of the efficacy in achieving better surgical and long-term outcomes. Additionally, we need correlative blood based and tumor studies tied to these prospective trials that can serve as biomarkers and help separate responders and long-term survivors from patients who do poorly regardless of therapy plan.

There is not a well-established standard of treatment for BRPC. Therefore, a patient that is identified as having a primary cancer with questionable resectability or locally advanced disease that may meet criteria for BRPC should be considered for treatment on research protocol and/or referral to a high-volume center with experience in treating this subset of disease. If this is not possible, patient should receive some form of neoadjuvant treatment.

A recommended treatment algorithm is outlined below in Fig. 6.3. If on presentation, a patient presents with clearly resectable disease, they should proceed to surgery or receive preoperative treatment on protocol. If presenting with BRPC, they should receive some form of preoperative treatment based on their ability to handle and desire for aggressive treatment. Either FOLFIRINOX or gemcitabine-containing multiagent regimens are reasonable treatment options.

Rational Study Endpoints for Preoperative Trials

A challenge encountered in designing preoperative trials involves identifying the most relevant endpoints for a trial. Commonly cited outcome measures in studies include response rate, percentage of patients undergoing resection, and rate of margin negative resection. However, many of these features do not adequately predict relapse or overall survival. Typically, systemic therapy alone or in combination with radiation results in minimal reduction in the primary tumor volume. Therefore, criteria that qualify a response based on reduction in tumor volume are typically not a useful endpoint. Likewise, the percentage of patients who proceed to surgery after neoadjuvant treatment is heavily influenced by patient and tumor characteristics. Indeed, a major benefit of neoadjuvant treatment is to avoid early surgical

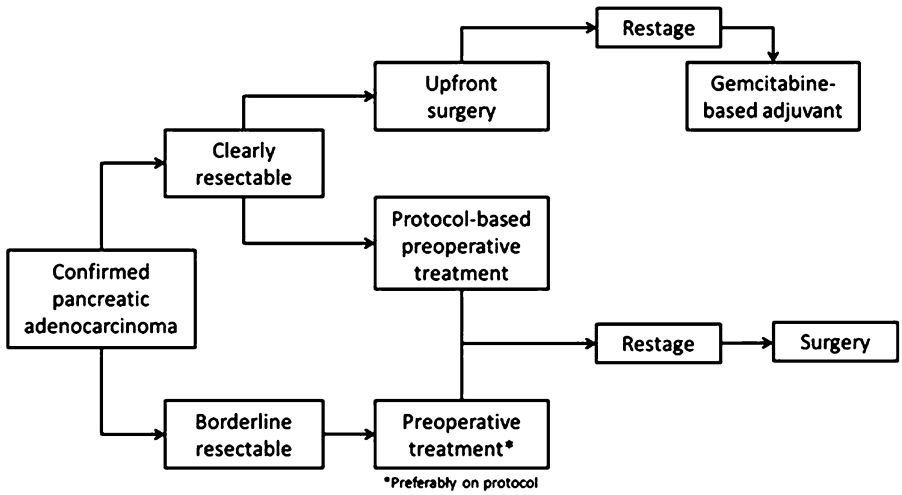

Fig. 6.3 Treatment algorithm

Table 6.2 Prospective trials with neoadjuvant chemotherapy in BRPC

Reference	BRPC cases	Regiment	Number resected (%)	R0 resection (%)	OS, all patients (mo)	OS, resected pts (mo)
Landry [89]	21	GEM + XRT versus GEM/Cis/5-FU then XRT	5	[a]	16.4	26.3
Sahora [34]	12	GEM + Docetaxel	8 (32 %)	87 %	[a]	16
Sahora [33]	15	GEM + OX	13 (39 %)	69 %	[a]	22
Pipas [90]	23	Cetuximab + GEM + XRT	25 (76 %)	92 %	[a]	24.3
Lee [35]	18	GEM + Cape	11 (61 %)	82 %	16	23
Kim [91]	39	GEM + OX + XRT; Adj GEM + OX	24 (62 %)	84 %	18	25
Motoi [92]	16	GEM + S1 (2c)	[a]	87 %	18	[a]
Takahashi [40]	80	GEM + XRT	43 (54 %)	54 %	19	25
Rose [93]	64	FOLFIRINOX (6c)	31 (48 %)	27 (87 %)	23.6	[a]
Takeda [94]	35	GEM + Hyperfract XRT	26	26	12.4	22
Esnaola [95]	13	GEM + OX + Cetuximab; then Cape + XRT	9	9	16.4	26.3

[a]Not provided

intervention in patients with microscopically advanced disease that will declare itself as inoperable. At the present time, it is not to predict which BRPC patients have microscopic advanced disease at diagnosis. Therefore, it is possible that failure to undergo surgical resection may not represent failure of preoperative systemic therapy. Finally, margin negative resection seems to correspond well with survival in the majority of retrospective and prospective studies reported (Tables 6.1 and 6.2). Margin status most directly is representative of local disease control, but seems to act as an indirect surrogate for metastatic disease control.

Additional endpoints and markers of disease response may improve our understanding of treatment efficacy and serve a predictive role. Ca 19-9 is a commonly expressed cell surface marker in pancreatic cancer cells. Decrease in either measured level or trajectory of Ca 19-9 is associated with a response to treatment [53, 54]. Moreover, there is data suggesting that Ca 19-9 may be important in prognostication. In a recent study from MDACC, normalization of Ca 19-9 after neoadjuvant therapy was associated with longer overall survival in both resected and unresected patients [55]. Conversely, failure of the Ca 19-9 level to normalize independently predicted shorter OS. A separate study found that while low baseline Ca 19-9 carried a positive predictive value of completing neoadjuvant treatment, this was limited by poor negative predictive value [56]. The authors also found little correlation between Ca 19-9 response and histopathologic response. Prospective studies that follow Ca 19-9 through the course of treatment are needed. There are several other potential serum-based testing methods for response to therapy that will be discussed in detail later in this chapter.

There is clear evidence that preoperative chemotherapy is effective in some patients. In BRPC cases, once inoperable patients are now being effectively treated with multimodality therapy and achieving cure. Measuring response to therapy is crucial to improving and designing new treatment regimens. However, most of these therapies require good performance status and are most effective when the full four to six treatment course is completed. To optimize treatment, there are several areas of patient care that should be addressed by both non-oncology physicians and other healthcare providers.

Considerations during Systemic, Preoperative Therapy

There are several important aspects of care that need to be optimized prior to initiation of chemotherapy; several are discussed in detail in previous

chapters. Broadly, both physical and emotional aspects of a patient's treatment should be systematically addressed. These include placing a metal biliary stent, prehabilitation for deconditioned patients, optimizing nutrition, and early discussion of patient expectations for experience during and effect of treatment.

Role of metal stents: Patients with pancreatic adenocarcinoma are often treated for biliary obstruction with endoscopic stent placement prior to evaluation by an oncologist. For resectable cancers, stent placement is not necessary when short-term surgical intervention will definitively address obstruction. Additionally, in patients who do not have symptoms of obstruction at diagnosis or have disease in the body or tail, biliary drainage may not be necessary. However, given the ambiguity of borderline resectable cases, pretreatment stenting is common. Plastic stents are commonly used in the treatment of malignant obstruction. This is due to concerns about intraoperative injury during transection of the common bile duct arising from use of uncovered metal stents [57]. Unfortunately, plastic stents have a greater tendency to become occluded and indeed have been found on to remain patent for less than the average amount of time required to complete neoadjuvant therapy [58]. Given that stent occlusion is likely to interrupt therapy and potentially result in life-threatening infection, it is preferable that all locally advanced pancreatic adenocarcinoma patients receive a metal stent [59]. Of importance, stent type should be determined prior to initiating therapy, and patients with plastic stents should undergo stent exchange prior to treatment.

Role of prehabilitation: Prehabilitation is a relatively new concept in the treatment of cancer and refers to enhancing a patient's functional capacity prior to medical or surgical intervention [60]. While the term originally applied to improving physical capacity, most prehabilitation programs are multidimensional and address debilitation, improving nutrition, optimizing comorbid conditions, and even psychosocial problems. Several trials of prehabilitation therapy have demonstrated impressive improvement in rates of postoperative recovery in colorectal cancer patients [61, 62] and chemotherapy tolerance in breast cancer patients [63]. It is increasing being recognized that patients with BRPC and marginal performance status and/or reversible comorbidities are at higher risk of poor outcomes [64]. The poor-risk BRPC patients who are most likely to benefit for prehabilitation should be identified and treated with a multidisciplinary approach that involves physical therapy, nutritional counseling, and medical or geriatric consultation and optimization.

Nutrition: A history of weight loss is common at presentation in many patients. Additionally, clues to pancreatic insufficiency should be sought such as a history of loose stools that float and may be foul smelling and diabetes history. Early initiation of pancreatic enzyme replacement and appetite stimulant is important prior to initiation of chemotherapy. Referral to a nutritionist may help a patient to identify and learn optimal eating habits throughout therapy.

Setting expectations: It is also essential to directly address patient expectations regarding the experience during neoadjuvant therapy and the chance of ultimately proceeding to surgical intervention. Most neoadjuvant regimens are aggressive and delivered in the outpatient setting. Multimodality treatment courses are long and patients should approach therapy like a marathon by addressing many of the issues above before starting. Complications, particular in high-risk patients, may interrupt or necessitate discontinuation of care. Even with evidence-based preoperative treatment, radiographic response and surgical exploration determine resectability [65]. It is essential that patients understand the risk that even with neoadjuvant treatment they may not be curable with surgery.

Biomarkers and Populations of Interest: Tested and Work in Progress

There are several critical points that need to be addressed to improve outcomes and quality of life with regard to neoadjuvant therapy in the BRPC population. Many questions remain regarding the optimal chemotherapy regimen, stratification of elderly and high-risk patients, length of treatment, and how to incorporate novel therapies. At the present time, we rely heavily on imaging to stage and track response to therapy. With increasing recognition of malignancy-related biomarkers, circulating tumor cells, or cell-free DNA (cfDNA), it will be critical to utilize such tumor markers to assess response to treatment. As previously discussed, Ca 19-9 is well established as marker of response to treatment [55]. Several novel markers are emerging that may help personalize chemotherapy choice in the future.

Human equilibrative nucleoside transporter 1 (hENT1) expression has been shown to correlate with gemcitabine-based therapy responsiveness and overall survival [66]. In addition to being an important cellular membrane transporter, its expression is also associated with the epithelial–mesenchymal transition (EMT) in pancreatic adenocarcinoma cells. In knockdown models, it appears to result in an altered cellular phenotype [67]. The recognition of this marker is significant as it allows recognition of tumors that may be resistant to standard gemcitabine-based therapies. A lipid conjugate of gemcitabine has been tested in a population with hENT1 expression, but was not found to be superior to standard gemcitabine therapy [68]. The ability to recognize a priori resistance to gemcitabine in the BRPC population will help to select the optimal regimen at the outset of treatment and potentially if resistance develops during treatment.

The secreted protein acidic and rich in cysteine (SPARC) is a protein that plays an essential role in the stromal microenvironment of pancreatic cancer. In PDAC, high levels of peritumoral fibroblast expression of SPARC in resected specimens resulted with significantly worse survival, with a hazard ratio of 1.89 [69]. Analysis of resectable patients from the CONKO-001 trial found that this increased mortality was restricted to patients who received adjuvant gemcitabine, suggesting resistance to gemcitabine [70]. In a separate study, adding nab-paclitaxel to gemcitabine resulted in the disruption of the stromal microenvironment and improved clinical outcomes [71]. These findings suggest SPARC expression could be used to better target chemotherapy to patients. However, a recent analysis of SPARC expression in the MPACT trial by Hidalgo [72] found conclusive evidence it was not predictive in advanced disease. The role of SPARC in clinical treatment of BRPC remains unclear.

There is evidence that the transforming growth factor beta (TGF-β) pathway plays an important role in pancreatic adenocarcinoma. The SMAD4 protein—also referred to as the DPC4 tumor suppressor gene—is an intracellular mediator of increased TGF-β pathway activity. While there are conflicting reports on the role of SMAD4 expression on overall survival [73, 74], a recent meta-analysis suggests it is correlated with overall poor prognosis [75, 76].

The role of liquid biopsies in pancreatic cancer is exciting as the quantity of tissue specimen that can be obtained presurgically is limited. There is some evidence that circulating tumor cells can be collected and cultured in pancreatic cancer [77, 78]. There is limited data evaluating circulating cfDNA, but it does appear across pancreatic inflammatory conditions; pancreatic adenocarcinoma has some of the highest detectable levels [79]. The ability to obtain circulating tumor cells and genetic material will be essential in monitoring response to therapy and ideally will contribute to understanding different response patterns among patients.

One important area of consideration is the tolerability of neoadjuvant therapy and completion rates, particularly in the elderly population. There is some controversy as to whether elderly patients have increased surgical complication rates [80]. However, studies from major centers suggest that age is not an independent variable in postsurgical morbidity [81, 82]. Therefore, it is important that elderly patients with BRPC complete neoadjuvant

therapy to optimize their chance for surgical resection and cure. One analysis suggests that BRPC patients over 75 years old are nearly three times less likely to complete neoadjuvant therapy than their younger counterparts [83]. A separate single-institution study of BRPC found similar R0 resection rates, 64.7 % versus 60 %, among older patients treated with FOLFOX and younger patients treated with FOLFIRINOX [84]. Indeed, age may be a less appropriate means of classification than a more comprehensive measurement of performance status and underlying comorbidities. Further studies are needed in elderly individuals to identify the optimal neoadjuvant treatment paradigm that balances efficacy with tolerability.

Conclusions

Neoadjuvant chemotherapy is an important component of the multimodal management of BRPC. There are ongoing efforts to improve outcomes of this aggressive disease through combination of multi-agent neoadjuvant chemotherapy regimens and novel therapeutic agents. Our perception of BRPC as being unpredictable highlights a gap in our understanding of the underlying biology of this disease. As we enter the era of individualized cancer therapy, it is important to identify novel markers of disease to better prognosticate and tailor therapies to patients. In the present, it is essential that all stakeholders work together to establish uniform consensus definitions and prospective trials to inform clinical practice.

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Role of Radiation Therapy

7

Neilayan Sen and Ross Abrams

Introduction and Overview

Complete surgical resection has long been a fundamental element of any curative intent paradigm for the treatment of localized pancreatic adenocarcinoma. Initial surgical series published in the 1960s–1980s showed significant morbidity and mortality (up to 30 %) associated with attempted resection [1, 2]. Subsequently, advances in surgical technique, diagnostic imaging, and perioperative care decreased surgical morbidity and mortality [3]. In addition, progress in the field of diagnostic imaging has allowed for presurgical evaluation of resectability and the detection of non-symptomatic metastatic disease. These distinctions have made it increasingly possible and important to understand the clinical differences and opportunities among patients presenting with metastatic and non-metastatic findings and especially the distinctions around extent of local disease. Although medical oncologists have often included both metastatic and locally advanced patients in chemotherapy trials, developments in preoperative staging and perioperative management have made it increasingly important to recognize which patients are not well served by a "chemotherapy-only" approach. These distinctions rely on currently available imaging for understanding the relationship of local disease to arterial and venous anatomy, clinical prognostic factors, and evolving appreciation of the clinical implications of identified molecular markers.

Although several retrospective series in the late 1990s and early 2000s showed the feasibility and efficacy of neoadjuvant chemoradiotherapy in potentially resectable disease, there is considerable difficulty in interpreting these data as the criteria for resectability were not consistent from series to series. Following the establishment of NCCN guidelines, and with collaboration among the American Hepato-Pancreato-Biliary Association, Society of Surgical Oncology, and Society for Surgery of the Alimentary Tract starting in the late 2000s, many institutions have published their series on neoadjuvant chemoradiotherapy using standardized criteria for resectability. A summary of resectability criteria is presented in Table 7.1.

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Table 7.1 Comparison of Americas Hepatopancreaticobiliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology (AHPBA/SSO/SSAT), MD Anderson, National Comprehensive Cancer Network (NCCN), and Intergroup radiographic definitions of borderline resectable pancreatic cancer

	AHPBA/SSAT/SSO	MD Anderson	NCCN 2012[a]	Intergroup trial
SMV-PV	Abutment[b], encasement[c], or occlusion	Occlusion	Abutment with impingement or narrowing	Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall, and/or reconstructable[d] occlusion
SMA	Abutment	Abutment	Abutment	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall
CHA	Abutment or short-segment encasement	Abutment or short-segment encasement	Abutment or short-segment encasement	Reconstructable[d], short-segment interface between tumor and vessel of any degree
Celiac trunk	No abutment or encasement	Abutment	No abutment or encasement	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall

SMV superior mesenteric vein, *PV* portal vein, *SMA* superior mesenteric artery, *CHA* common hepatic artery
[a]The NCCN criteria have changed over the years. The most recent criteria (2.2012) are included
[b]Defined as tumor-vessel interface less than 180° of vascular circumference
[c]Defined as tumor-vessel interface at least 180° of vascular circumference
[d]Normal vein or artery proximal and distal to the site of suggested tumor-vessel involvement suitable for vascular reconstruction

Prognostic Factors for Survival in Locally Advanced Pancreatic Cancer

Clinical parameters at time of diagnosis have long been demonstrated as prognostic factors in patients with locally advanced and metastatic pancreatic cancer. A representative analysis of 335 patients with histologically confirmed pancreatic cancer (36 % of whom had localized or locally advanced disease) showed poor performance status (ECOG PS 2–4) and weight loss >10 % were independently associated with shorter overall survival [4]. Similarly, a high Charlson age-comorbidity index >3 at presentation and weight loss >10 % during neoadjuvant chemoradiotherapy are independently associated with reduced survival after resection [5, 6].

More recently, perioperative serum carbohydrate antigen (CA) 19-9 has been demonstrated as a prognostic marker for outcome after definitive resection independent of adjuvant therapy [7–9]. CA 19-9 has also been shown to be a useful marker in the treatment of patients with metastatic pancreatic cancer [10, 11]. These developments have spurred interest in the incorporation of CA 19-9 monitoring in the neoadjuvant setting. In an analysis of 141 patients with borderline resectable pancreatic cancer treated with neoadjuvant therapy (NAT) at MD Anderson, 82 % experienced measurable decline in CA 19-9 over the course of NAT. Sixty percent of all patients underwent resection. The normalization of CA 19-9 after NAT was associated with longer median overall survival among both non-resected (15 vs. 11 months) and resected patients (38 vs. 26 months). In multivariate analysis, failure to normalize CA 19-9 was independently associated with reduced survival (hazard ratio 2.13). In a similar analysis reported by investigators at the University of Pittsburgh, following NAT, a CA 19-9 response of >50 % predicted for R0 resection

(odds ratio 4.2) in a cohort consisting of 21 resectable, 40 borderline resectable, and 17 locally advanced presentations [12]. None of five borderline patients with an increase in CA 19-9 after NAT underwent R0 resection compared to 80 % of the remaining borderline resectable patients. Also, CA 19-9 response of >50 % independently predicted for improved survival (median overall survival 28 vs. 11.1 months).

Brief Review of Published Data on the Use of Radiotherapy in the Neoadjuvant Setting

Progress in the neoadjuvant management of borderline resectable pancreatic cancer has occurred in parallel with emerging data in the management of locally advanced and metastatic pancreatic cancer. In this section, relevant radiation therapy data are reviewed chronologically.

Early Investigational Approaches: External Beam Radiation as the Only Component of NAT (1970–1980s)

The rationale for neoadjuvant radiotherapy was first established in the 1970s after a seminal review of patterns of failure in patients treated with definitive surgery at Massachusetts General Hospital [13]. In 31 patients treated with radical surgery alone, 50 % had a local recurrence at time of death or last follow up. It was suggested from this analysis that radiotherapy after resection may improve cancer related survival and that preoperative radiotherapy could increase resectability. The feasibility of neoadjuvant radiotherapy was also established in the 1970s [14]. A representative early series of 17 patients reported successful radical operation in six patients after 40–50 Gy to the region of the pancreatic head. Analysis of resected specimens after preoperative radiotherapy showed severely degenerative cancer cells were more likely to be located at the advancing point of carcinoma providing a histopathologic basis for the theory of improving resectability [15]. The technique of preoperative radiotherapy gained institutional popularity in the 1980s [16]. One of the first published series reported on 54 consecutive patients deemed appropriate candidates for curative intent resection. Twenty-three patients were managed with neoadjuvant radiotherapy (50 Gy in 25 fractions with anterior-posterior parallel opposed portals to an average field size of 11×11 cm). These patients were compared to 31 patients who proceeded to immediate laparotomy. Although there was no difference in resectability between the two groups, 1 year survival was significantly improved and death due to regional recurrence within 1.5 postoperative years was less common (75 % vs. 43 %, $p<0.05$). However, long-term survival was not affected [17]. In sum, these data suggest that after preoperative radiotherapy, a potential survival benefit from improved local regional control was overwhelmed by systemic failure.

Pre-gemcitabine-Based Chemoradiotherapy

Investigators at MD Anderson initiated a series of NAT protocols in the late 1980s. Technical feasibility and safety of this paradigm was established in 1992 with 28 patients with adenocarcinoma of the pancreatic head all of whom received preoperative radiotherapy (50.4 Gy) and concurrent daily fluorouracil [18]. All 28 patients completed the prescribed course of neoadjuvant therapy—five patients demonstrated metastatic disease at re-staging 4–5 weeks after completion of chemoradiotherapy and 23 underwent laparotomy. Six patients were not resected after laparotomy due to unsuspected metastatic disease found at laparotomy (three) or locally advanced unresectable disease (three). Seventeen patients successfully underwent pancreaticoduodenectomy with one perioperative death. The technical feasibility of electron beam intraoperative radiotherapy to the postoperative bed after pancreaticoduodenectomy was established soon thereafter [19]. The results of these two prospective studies laid the groundwork for

a third prospective trial in which 39 patients received neoadjuvant chemoradiotherapy (30–50.4 Gy with daily 5-FU) and intraoperative radiotherapy (10 Gy with electron beam). Isolated local or peritoneal recurrences were documented in only 11 %, whereas 53 % developed liver metastases.

In parallel with the early prospective trials conducted at MD Anderson, investigators at Fox Chase performed a prospective feasibility study utilizing NAT prior to attempted resection of locally advanced pancreatic and periampullary carcinoma [20]. Thirty-four patients were treated with infusional 5-FU, bolus mitomycin-C, and radiotherapy (median 50.4 Gy). Twenty-five patients underwent exploration of whom 11 had liver or peritoneal metastases and 10 had potentially curative resections (R0 resections). Four of the 10 with potentially curative resections had previously unresectable disease based on laparotomy prior to neoadjuvant therapy. One patient died in the postoperative period. The promising results of this pilot study prompted an Eastern Cooperative Oncology Group phase II study of preoperative chemoradiotherapy for potentially resectable adenocarcinoma of the pancreas [21]. In this multi-institutional trial, 53 patients received NAT (50.4 Gy in 28 fractions with mitomycin 10 mg/m^2 on day 2 and 5-FU continuous infusion days 2–5 and 29–32). Six patients developed distant metastases at re-staging after neoadjuvant therapy. Forty-one patients ultimately underwent surgery and six of these patients had local tumor not amenable for curative intent resection. Twenty-four patients underwent resection and the median survival for this group was 15.7 months.

After the feasibility and safety of 5-FU-based NAT was established for resectable patients, individual institutions began to systematically employ a neoadjuvant treatment paradigm for patients with questionably resectable disease. Many of the initial series investigating the role of NAT in the management of pancreatic cancer included 5-FU and mitomycin-C as radiosensitizers. A representative series from Stanford reported on 15 patients with "marginally" resectable adenocarcinoma of the pancreatic head (portal vein, superior mesenteric vein, or superior mesenteric artery involvement as identified by CT). Patients received external beam radiotherapy (50.4–56 Gy) with concurrent protracted venous infusion of 5-FU (250 mg/m^2 per day). No patient experienced grade 3 toxicity during neoadjuvant therapy. Nine of the 15 patients underwent R0 pancreaticoduodenectomy [22]. The median survival for resected patients was 30 months. In 2001, investigators at Duke reviewed a series of 111 patients with localized pancreatic cancer treated with neoadjuvant 5-FU-based chemoradiotherapy (median 45 Gy) [23]. Tumors were defined as locally advanced with any arterial involvement or venous occlusion by computed tomography. The overall R0 resection rate was 72 and 19 % of patients with initially locally advanced carcinoma ultimately underwent resection.

Development of Gemcitabine-Based Chemoradiotherapy

In parallel with the development of neoadjuvant therapy protocols, gemcitabine gained popularity as an active agent in the management of advanced or metastatic pancreatic cancer and was shown in a randomized setting to prolong survival in comparison to 5-FU [24]. These data challenged the use of 5-FU-based chemotherapy in the management of locally advanced disease. In the same time frame, rapid technological advancements in the field of radiation oncology were occurring. Particularly, the advent of 3D conformal planning and intensity modulated radiotherapy (IMRT) allowed for the possibility of dose escalation while minimizing risk of acute and chronic gastrointestinal toxicity.

From preclinical trials, gemcitabine was known to be a potent radiosensitizer [25]. This prompted a series of phase I trials for locally advanced/unresectable pancreatic cancer which proved that moderate dose hypofractionated RT to conventional (historical) treatment volumes (regions of primary tumor and draining lymph nodes including para-aortic nodes) with concurrent full dose gemcitabine produced

unacceptable rates of gastrointestinal toxicity [26–28]. Efforts at mitigating this toxicity took several approaches. One was to reduce both the volume of tissue irradiated and to reduce the number of fractions and dose per fraction of radiotherapy when using full dose gemcitabine. Using this approach, investigators at the University of Michigan recommended a dose of 36 Gy in fifteen 2.4 Gy fractions to gross tumor only. Subsequently these investigators extended this approach to 67 patients with locally advanced unresectable pancreatic cancer [29]. Of the 17 who ultimately underwent surgical exploration nine underwent resection (6 R0, N0).

This approach also provided the basis for a multi-institutional phase II trial in the early 2000s [30] in which 20 patients were treated with gemcitabine/RT with neoadjuvant intent (weekly gemcitabine 1000 mg/m^2 on weeks 1 and 2, 36 Gy in 15 fractions (using 3D planning) with weekly gemcitabine 1000 mg/m^2 on weeks 4–6, followed by weekly gemcitabine 1000 mg/m^2 on weeks 8 and 9). Importantly, this is the first multi-institutional trial in which patients were prospectively evaluated for degree of resectability according to national or cooperative group guidelines. All 20 patients were deemed to have potentially resectable disease (six borderline resectable). Borderline cases were confirmed by endoscopic ultrasound or magnetic resonance imaging. 19 of 20 patients completed neoadjuvant therapy without interruption. Twenty underwent operative exploration of whom 17 were resected. The R0 resection rate was 94 % and at a median follow up of 18 months, 41 % remained alive and free of disease.

In contrast to early data with full dose gemcitabine, reduced dose gemcitabine was shown to be tolerable with more conventional radiotherapy treatment volumes and dose. In 2009, a large series from Germany reported on 120 patients with borderline or unresectable tumors [31], based on computed tomography by NCCN criteria. Patients received 55.8 Gy to the primary tumor and 50.4 Gy to regional nodes. A majority of patients received concurrent gemcitabine (300 mg/m^2 on weeks 1, 2, 4, and 5) and cisplatin (30 mg/m^2 on weeks 1, 2, 4, and 5). No subsequent chemotherapy was administered. 31.7 % underwent resection, among whom 95 % underwent R0 resection. Forty-seven percent had primary tumor downstaging (pathologic T stage in comparison to clinical T stage by computed tomography) and 24 % had upstaging. Median disease-specific survival for patients with R0 resection was 52 months in comparison to 11 months for patients with R1 resection.

The second multi-institutional prospective trial (E1200) of neoadjuvant therapy for prospectively defined borderline resectable pancreatic cancer was published in 2010 [32]. In this two-arm randomized phase II trial, patients with potentially resectable pancreatic cancer (defined as tumor abutting the portal vein or superior mesenteric vein, abutting the hepatic or superior mesenteric artery, extending to the origin of the gastroduodenal artery, or occluding the superior mesenteric vein <2 cm) were randomized to one of two NAT arms. In the first arm, patients received preoperative radiotherapy (50.4 Gy to gross tumor +2 cm margin with 3D planning) with concurrent gemcitabine (500 mg/m^2 weekly). In the second arm, the same radiotherapy regimen was prescribed with concurrent gemcitabine, cisplatin, and 5-FU. In both arms, following surgery, maintenance therapy of gemcitabine 1000 mg/m^2 for seven cycles was prescribed. Ten patients were enrolled in the first arm and 11 patients were enrolled in the second arm. Three patients in the first arm and two patients in the second arm underwent resection (total R0 resection rate of 60 %). Grade 4 toxicity was significant and more common in the first arm (36 % vs. 18 %). The median overall survival of resected patients was 26.3 months.

The largest single institution analysis of patients with systematically defined borderline resectable pancreatic cancer treated with neoadjuvant intent was performed by investigators at MD Anderson [33]. In this analysis, patients were separated into three types. Type A patients had borderline tumor anatomy with respect to regional vasculature based on CT (≤180° abutment of SMA or celiac axis, tumor abutment or encasement of a short segment of the hepatic artery, or short-segment occlusion of the SMV,

PV, or SMV-PV confluence amenable to vascular resection and reconstruction). Type B patients had possible extrapancreatic metastatic disease (including those with biopsy proven N1 disease). Type C patients had marginal performance status or severe medical comorbidities. One hundred and sixty patients (7 %) of all patients diagnosed with pancreatic adenocarcinoma were classified as having borderline resectable disease based on these criteria. Eighty-four of these patients were type A and all received neoadjuvant chemotherapy with or without radiotherapy (50.4 Gy in 28 fractions or 30 Gy in 10 fractions using 3D planning with concurrent 5-FU, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses). Thirty-eight percent of these patients ultimately underwent resection with a 97 % R0 resection rate. Full dose concurrent gemcitabine was not used in this population. All resected patients had been treated with neoadjuvant chemoradiotherapy. Median survival for patients who underwent resection for Type A tumors was 40 vs. 15 months for those who did not undergo resection. Median overall survival of all 84 patients with Type A tumors was 21 months. Importantly, included in this population of patients was a cohort of borderline resectable patients treated with 4 field 3D conformal radiotherapy to 30 Gy in 10 fractions with large fields encompassing the regional nodes with concurrent reduced dose gemcitabine. Twenty-seven percent of these patients experienced severe toxicity (defined as prolonged hospitalization, GI bleed, more than 3 dose deletions of gemcitabine, discontinuation of 5-FU, or grade 5 toxicity). This cautionary experience highlights the importance of highly conformal radiotherapy (that is, reduced volumes of normal tissue irradiated, especially stomach and small bowel) even with reduced dose gemcitabine.

A recent prospective trial by Leone et al. in 2013 [34] demonstrated the feasibility of induction gemcitabine/oxaliplatin (GEMOX) prior to reduced dose gemcitabine and concurrent radiotherapy for patients with locally advanced and borderline resectable pancreatic cancer. Thirty-nine patients were enrolled in this study, of whom 15 had borderline resectable disease (by MD Anderson criteria). Patients received four cycles of GEMOX prior to re-staging in preparation for chemoradiotherapy. Twelve of 15 patients with borderline disease proceeded to chemoradiotherapy (50.4 Gy in 28 fractions using 3D planning). Nine of these 12 patients underwent resection and this group had a median overall survival of 31.5 months.

Advances in Radiation Delivery and the Integration of Full Dose Concurrent Gemcitabine-Based Chemotherapy

Given reports on the efficacy of full dose gemcitabine-based combination chemotherapy in the advanced setting, the importance of obtaining systemic control in the neoadjuvant setting was reinforced. A phase I study conducted at the University of Michigan showed the safety of the addition of oxaliplatin to full dose gemcitabine and radiotherapy for resectable and unresectable pancreatic cancer [35]. This prompted a multi-institutional phase II trial headed by Kim et al. [36] in which 68 patients with localized pancreatic adenocarcinoma were treated with gemcitabine/oxaliplatin and radiotherapy with neoadjuvant intent. Patients received two cycles of neoadjuvant gemcitabine (1000 mg/m^2 on days 8, and 15) with oxaliplatin (85 mg/m^2 on days 1 and 15) with 30 Gy in 15 fractions (to small fields encompassing a clinical target volume defined as gross disease +1 cm margin). Two cycles of adjuvant chemotherapy were given after resection. Resectability was defined radiographically according to NCCN criteria. Ninety percent completed the prescribed course of neoadjuvant therapy. At presentation, 23 patients had resectable disease, 39 had borderline resectable disease, and six had unresectable disease. Of the 39 patients with borderline disease, 30 underwent laparotomy and 24 underwent resection (62 %). Three of these 39 patients developed local progression on re-staging prior to surgery and one developed distant progression. Of note, of the 23 patients with NCCN resectable disease at presentation, two developed distant progression at

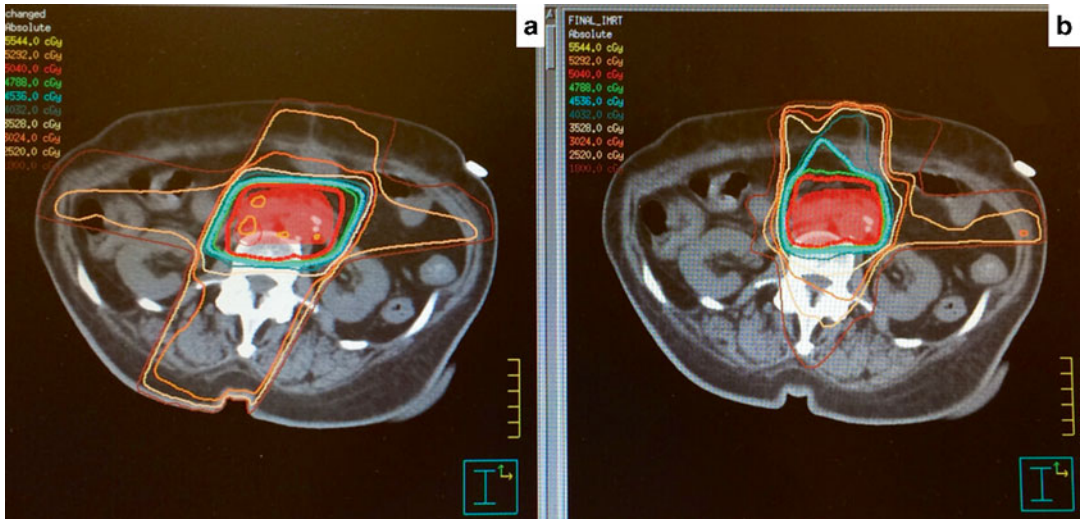

Fig. 7.1 3D conformal radiotherapy (**a**) vs. IMRT (**b**). Note increase in conformal target coverage and decrease in high dose to adjacent organs at risk

re-staging prior to resection (8.7 %). The overall R0 resection rate was 84 % and 13 of 19 patients with SMA/celiac axis contact underwent R0 resection (68 %). Median survival for patients undergoing R0 resection was 34.6 months and median survival of 28 patients with borderline disease who underwent resection was 25.4 months. Of patients who underwent R0 or R1 resection, local recurrence as a component of first failure was 29 %. On multivariate analysis, incomplete resection (R1/2) was associated with decreased survival (HR 1.2).

In the early 2000s, IMRT became widely available. Advantages of IMRT over conventional 3D planning include highly conformal target coverage and sparing of adjacent organs allowing potential dose escalation and facilitating full dose, highly active systemic therapy with gemcitabine. Comparison of IMRT to 3D planning to illustrate these points is shown in Fig. 7.1.

A phase I/II trial also conducted at the University of Michigan established the safety and efficacy of full dose gemcitabine and dose escalated IMRT in the locally advanced setting [37]. In this trial, a dose of 55 Gy in 25 fractions with concurrent full dose gemcitabine (1000 mg/m^2 on days −22, −15, 1, 8, 22, and 29) was found to be the maximal tolerated radiotherapy dose with a 24 % probability of grade 3 or higher GI toxicity but also yielding an impressive 59 % 2-year local failure free survival.

Retrospective reports of the safety and efficacy of concurrent full dose gemcitabine-based chemoradiotherapy have also recently been published by others. Investigators at Osaka Medical center reported their retrospective results of NAT for borderline resectable pancreatic cancer in 2013 [38]. Of 268 patients treated with gemcitabine-based chemoradiotherapy, 80 had borderline resectable tumors (based on MD Anderson criteria). Patients received 50 Gy in 25 fractions to the primary tumor and regional lymph nodes using 3D conformal planning techniques and full dose gemcitabine (1000 mg/m^2 weekly × three of every 4 week cycle for three cycles). 99.6 % completed the prescribed course of radiotherapy. For all patients, the most common toxicity was leukopenia (grade 3 47.4 %) and grade 3 GI toxicity was uncommon (3 %). Fifty-four percent of patients with borderline resectable disease underwent resection with 98 % R0 resection rate. Five-year survival for patients who underwent resection with resectable disease at presentation was 57 % vs. 34 % for patients with borderline disease. Although this represents a highly selected patient population, survival in

this series compares favorably to patients treated with adjuvant chemotherapy alone in randomized settings. Nodal involvement and borderline resectability at presentation were significantly associated with poorer survival after resection on multivariate analysis. Importantly, adjuvant chemotherapy was not administered in this series.

Alternative concurrent chemotherapeutic agents: Although gemcitabine has gained considerable popularity as a concurrent agent during radiotherapy given its radiosensitization and highly active systemic properties, other radiosensitizers are being investigated. For example, Esnaola et al. reported on a phase II trial of induction gemcitabine, oxaliplatin, and cetuximab followed by capecitabine-based chemoradiotherapy for patients with locally advanced or borderline resectable pancreatic cancer [39]. Patients received six cycles of induction chemotherapy followed by chemoradiotherapy consisting of IMRT with a simultaneous integrated boost technique (45.9 Gy in 30 fractions to elective nodal regions and 54 Gy in 30 fractions to gross tumor). Daily concurrent capecitabine (800 mg/m^2 BID) was prescribed on days of radiotherapy. Thirty-nine patients were enrolled and 69.2 % of all patients with borderline resectable disease (by NCCN criteria) achieved R0 resection.

Proton Therapy and SBRT in the Neoadjuvant Setting

An alternate approach to integrating radiotherapy and chemotherapy regimens not yet tested in the concurrent setting would be to use a very abbreviated course of radiotherapy sequentially with the intended systemic regimen. A five fraction regimen of accelerated hypofractionated radiotherapy has been shown to be effective in decreasing local recurrence in the neoadjuvant treatment of rectal cancer [40]. However, dose escalation and hypofractionation for pancreatic tumors are complicated by adjacent radiosensitive dose limiting structures such as the duodenum, stomach, small bowel, and kidneys. A dosimetric feasibility study at Massachusetts General Hospital showed that target coverage with proton beam radiotherapy was comparable to IMRT while mean dose (as a percentage of prescription dose) to kidney, liver, and small bowel were significantly improved [41]. This provided the impetus for a recently reported phase I/II trial investigating preoperative chemoradiotherapy for resectable pancreatic cancer with an accelerated hypofractionated course of proton beam radiotherapy [42]. The phase II dose was established at 5 daily doses of 5 Gy with concurrent capecitabine. Resected patients received adjuvant gemcitabine. There were two grade 3 toxicities and no grade 4 or 5 toxicities during chemoradiotherapy. Thirty-seven of 48 eligible patients underwent resection. Locoregional failure occurred in 16.2 % and distant recurrence occurred in 72.9 %. Proton beam radiotherapy as a component of neoadjuvant therapy for borderline resectable pancreatic cancer has not yet been reported.

Stereotactic body radiotherapy (SBRT) is a highly conformal treatment modality that requires precise diagnostic imaging capability, precise immobilization, and daily image guidance. Advantages include highly conformal treatment delivery with a sharp dose fall off in comparison to traditional 3D conformal or IMRT planning techniques (see Fig. 7.3). SBRT has been shown to be effective in obtaining local control in patients with unresectable locally advanced disease [43–45]. However, the use of SBRT in the neoadjuvant setting for borderline resectable pancreatic cancer remains investigational. Based on safety/tolerability and local control data for patients with unresectable disease, investigators have also examined the role of SBRT in the neoadjuvant setting. In 2013, Chuoung et al. reported on a series of 73 patients with unresectable or borderline resectable (by NCCN criteria) pancreatic cancer treated with induction chemotherapy followed by SBRT with neoadjuvant intent [46]. Median doses of 35 and 25 Gy were delivered to the region of vessel involvement and to the remainder of the tumor over five consecutive fractions. Thirty-two patients with borderline disease underwent surgery (56.1 %) and 31 achieved an R0 resection (96.9 %). These 31 patients had a median overall survival of 19.3 months.

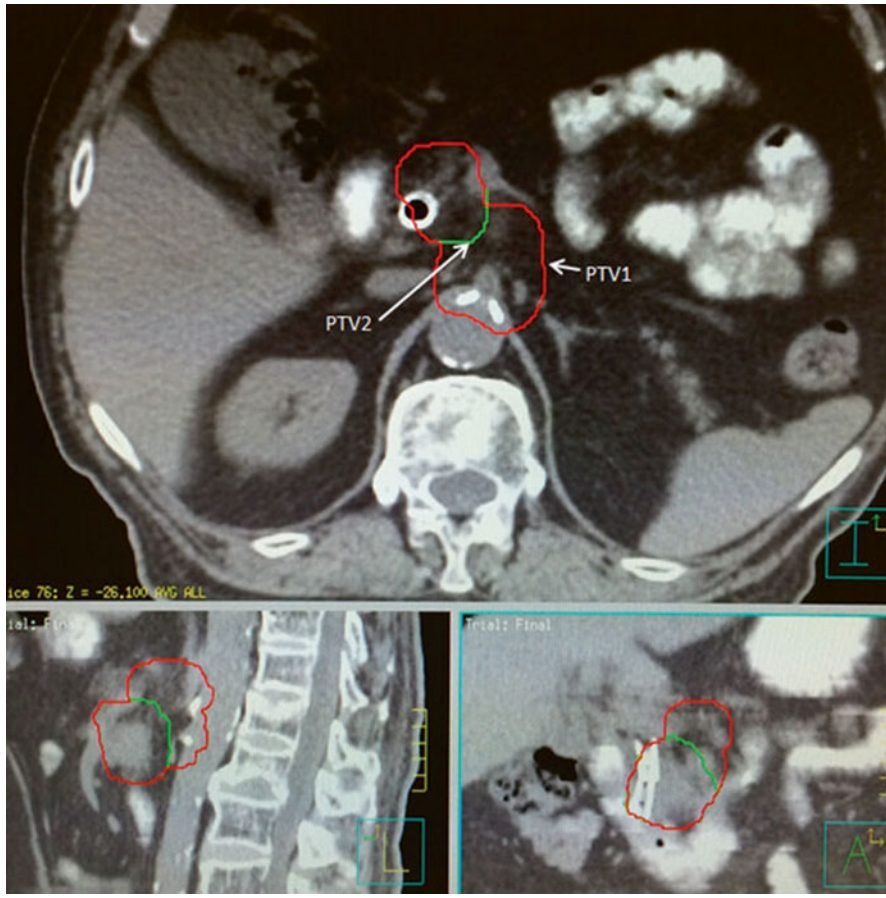

Fig. 7.2 Planning target volumes (PTVs) with and without regional nodes. *PTV1* with regional nodes, *PTV2* without regional nodes

Late grade 3 toxicity was minimal (5.3 %). In 2015, Moningi et al. reported the Johns Hopkins experience on 88 patients with locally advanced and borderline resectable pancreatic cancer (defined according to SSO guidelines) treated with SBRT [47]. Seventy-four patients had locally advanced unresectable disease and 14 of these patients had borderline resectable disease. Patients received a total dose of 25–33 Gy in five fractions (PTV = GTV + 2–3 mm, gold fiducials placed in tumor). Institutional constraints for stomach and small bowel dose were employed. Most patients received pre-SBRT chemotherapy—19 patients ultimately underwent resection (79 % locally advanced at presentation) and 84 % had R0 resections. Resected patients had median survival of 20.2 months after SBRT. Late GI toxicity after SBRT was uncommon (5 % grade 3).

Molecular biology and selection of patients forneoadjuvant treatment with curative intent: Although R0 resection is universally accepted as a critical component of treatment with curative intent, the 5-year overall survival with completely resected pancreatic cancer remains poor (20–25 %). Resection after neoadjuvant therapy is associated with improved survival in two meta-analyses (see Tables 7.2 and 7.3). However, isolated locoregional recurrence is rarely a cause of cancer-specific mortality in this population. The tumor biology driving lymphovascular invasion and subsequent distant metastatic spread is believed to be distinct from the drivers for local growth. This concept is particularly relevant in the neoadjuvant treatment setting for borderline resectable pancreatic cancer and an understanding of tumor biology may, in the

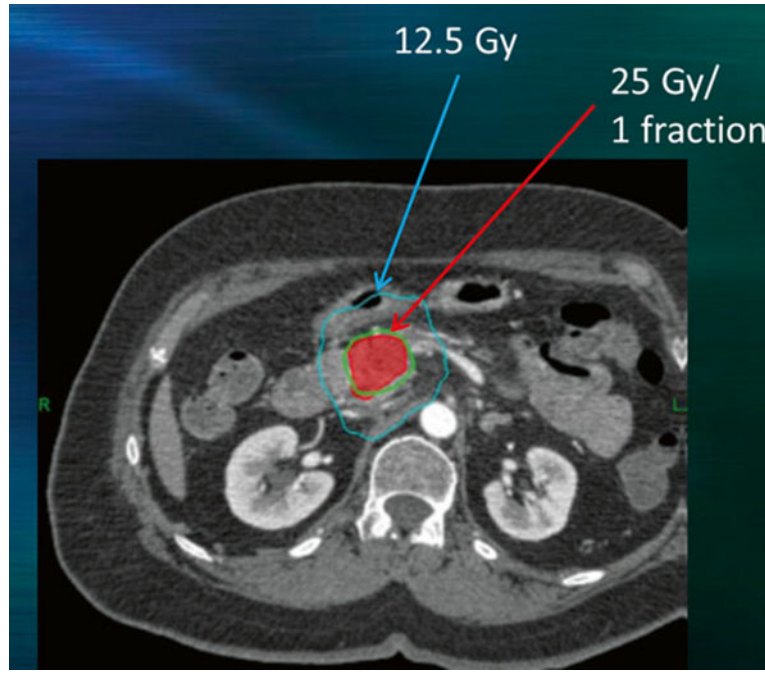

Fig. 7.3 SBRT allows for extreme hypofractionation with sharp dose gradient

Table 7.2 Neoadjuvant chemoradiotherapy meta-analyses: resection is associated with improved survival

	Morganti et al. [86]	Festa et al. [87]
Population	Unresectable at presentation	Borderline resectable at presentation
Resection rate (%)	27	55
Median survival of resected patients	23.6 months	22 months
Long-term survival	43 % at 3 years	44 % at 2 years
Median survival of unresected patients	10 months	10 months

future, allow for the selection of appropriate patients a priori.

Epithelial neoplasms must downregulate cell–cell adhesion structures in order to penetrate the basement membrane and metastasize [48]. This process bears resemblance to the epithelial mesenchymal transition (EMT) which is a crucial step in gestational development. In epithelial neoplasms, loss of E-cadherin is a fundamental step in an EMT-like process and allows for the transition of preneoplastic/neoplastic cells across the basement membrane. In support of this, partial or complete loss of E-cadherin expression in resected tumors is an independent predictor of poor outcome after definitive surgery [49]. Although mutations within the E-cadherin gene are rarely found, E-cadherin downregulation may occur through epigenetic pathways and upregulation of certain transcriptional factors have been shown to be associated with early metastasis [50, 51].

The TGF-beta signaling pathway is a key regulator of cellular proliferation and angiogenesis [52]. Alterations within this pathway are commonly reported in pancreatic cancer cell lines [53]. SMAD4 (Dpc4) is a tumor repressor in the TGF-beta signaling pathway and is commonly inactivated in pancreatic adenocarcinomas. Loss of SMAD4 expression independently correlates with worse survival after definitive resection [54, 55]. In addition, expression of SMAD4 correlates with local recurrence rather than distant dominant disease progression after chemoradiotherapy in patients with locally advanced unresectable cancer [56]. Importantly, in patients with resectable

Table 7.3 Selected prospective neoadjuvant chemoradiotherapy trials for borderline resectable pancreatic cancer

References	Resectability criteria	Patients with BRPC	Pre-op regimen	Resection rate (%)	R0 resection rate (of patients resected) (%)	OS in patients with resected BRPC
Kim et al. [36]	NCCN	39	Gem/Ox + RT (30 Gy)	62	84	25 months
Leone et al. [34]	MD Anderson	15	Gem/Ox → Gem + RT (50.4 Gy)	60	82[a]	31.5 months
Esnaola et al. [39]	NCCN	13	Gem/Ox/ Cetux → Cape + RT (54 Gy)	69	100	24.1 months[b]
Crane et al. [56]	MD Anderson	18	Gem/Ox/ Cetux → Cape + RT (50.4 Gy)	50	100	NR
Small et al. [30]	NCCN	10	Gem/Bev + RT (36 Gy/15 fx)	30	NR	NR

BRPC borderline resectable pancreatic cancer, *OS* median overall survival, *Gem* gemcitabine, *Ox* oxaliplatin, *Cetux* cetuximab, *Cape* capecitabine, *NR* not reported

[a]Includes patients with unresectable disease at presentation

[b]Includes patients with BRPC not resected, for resected BRPC median OS not reached

disease, immunohistochemical staining for SMAD4 on preoperative biopsy correlates with postoperative staining. In one series, loss of SMAD4 was associated with a six times higher likelihood of developing distant metastases after definitive resection [57]. A driver for angiogenesis may be rapid growth leading to areas of hypoxia within the tumor. Hypoxia-inducible factor 1 (HIF-1) is a transcriptional complex which increases angiogenic signaling in a hypoxic environment. High HIF-1 expression in resected pancreatic adenocarcinoma specimens is an independently significant predictor of distant failure vs. isolated local failure after resection [58].

Predictors for Response to Neoadjuvant Chemoradiotherapy

Computed tomography (CT) remains the most widely used modality for assessment of resectability prior to surgical exploration after NAT [59]. Complete regression of tumor with major vascular involvement by CT is uncommon after chemoradiotherapy [60]. RECIST responses are rare and do not correlate with survival [61]. Regardless, partial regression on CT is occasionally seen and can be described based on tumor/vasculature relationship and gross volume. One-, two-, and three-dimensional methods of assessment may all be appropriate [62]. Extent of tumor/vein circumferential interface (none, ≤180°, >180°) following chemoradiotherapy is predicted for SMV or PV resection in a large series [63]. Partial regression of gross tumor on CT correlates with resectability in several series [59, 62]. Cassinotto et al. reported a series of 47 patients with locally advanced pancreatic adenocarcinoma who were resected after neoadjuvant chemoradiotherapy [59]. Partial regression of tumor contact with any peripancreatic vascular axis was associated with R0 resection in 91 % of cases. Persistent SMV or portal vein stenosis was not predictive of R1 resection after chemoradiotherapy.

Although regression on CT may predict for resectability, lack of regression does not predict for unresectability [35]. Additionally, CT detected response to chemoradiotherapy may not manifest for months after initiation of radiotherapy [64]. This may be due to the lack of ability of CT to differentiate stromal changes secondary to desmoplastic reaction from true viable tumor [65]. In 2015, investigators at Massachusetts General Hospital reported their experience using CT to predict resectability after FOLFIRINOX in

the neoadjuvant setting. Of 40 patients with locally advanced/borderline resectable pancreatic cancer (by AHPBA/SSO/SSAT guidelines) 26 were classified as locally advanced and 14 as borderline resectable. Following FOLFIRINOX, re-staging CT showed 19 locally advanced and 9 borderline. Ultimately, all 40 underwent resection with an overall 92 % R0 resection rate [66].

Since radiographic regression is not common after neoadjuvant therapy, there is considerable interest in evaluating serum tests as predictors of response. In 2014, Boone et al. reported on a series of 78 patients (40 borderline) who were treated with neoadjuvant chemotherapy ± radiotherapy [12]. Seventy-two percent had a decrease in serum CA 19-9 >50 % with neoadjuvant treatment. In borderline resectable patients, CA 19-9 reduction >50 % predicted for R0 resection (OR 4.2). Five patients with borderline resectable disease had an increase in CA 19-9 and none underwent R0 resection. CA 19-9 response >50 % was an independent predictor of survival (median overall survival 28 vs. 11.1 months). Tzeng et al. reported a series of 141 patients treated with neoadjuvant chemotherapy and chemoradiotherapy over a 10-year period in 2014. For patients who underwent resection following neoadjuvant therapy, the positive predictive value of a decline and the negative predictive value of an increase in CA 19-9 were 70 and 88 %. Normalization of CA 19-9 (<40 U/mL) following neoadjuvant therapy was associated with prolonged survival in both non-resected and resected patients.

In addition to serum CA 19-9, pathologic features at time of surgery after NAT predict for survival. In one study of 240 patients who received NAT and pancreaticoduodenectomy, posttreatment pathologic stage, pathologic tumor response, microscopic vascular involvement, lymph node positivity, and perineural invasion were significant prognostic factors [67]. On multivariate analysis, posttreatment pathologic stage and number of positive lymph nodes were independent prognostic factors [68]. In a prior analysis of 212 of these patients, tumor invasion into muscular vessels correlated with higher rates of R1 resection, lymph node positivity, and locoregional/distant recurrence [69].

Principles of Radiation Therapy

Patients should undergo CT simulation (scan covering the entire abdominal contents to the pelvic brim using 2–3 mm slice thickness) in the supine position with intravenous and oral contrast in order to accurately define the tumor and adjacent normal structures (NCCN guidelines). For patients with renal compromise, allergy to IV contrast, and when a fully enhanced and technically adequate diagnostic scan (CT or MRI) has recently been obtained, planning can be facilitated by importing and fusing these images into the patient's treatment planning images in the planning system. Patient immobilization should be maximized with the use of an alpha cradle, vac-lok, or equivalent device and arms should be positioned above the head. Gastric distension should be accounted for during simulation and treatment. Patients should be instructed to forego food or drink 2 h before simulation and daily treatment in order to reliably reproduce intraabdominal anatomy. 4D simulation is strongly recommended for all cases as substantial variation in pancreatic tumor position (particularly in the superior-inferior plane) can occur during the respiratory cycle [70].

Although regional nodal irradiation is commonly performed in the adjuvant setting, there is controversy regarding its incorporation in the neoadjuvant/borderline setting. Isolated nodal failure after neoadjuvant chemoradiotherapy and successful resection has not been reported. However, interpretation of available data is complicated by the lack of clearly defined radiation target volumes in many retrospective series. Omission of elective nodal irradiation in the locally advanced/unresectable setting does not appear to influence locoregional control or survival [71, 72]. In a series of 69 patients treated with neoadjuvant chemoradiotherapy with elective nodal irradiation performed in all patients at the Medical College of Wisconsin, 12.5 % of resected patients experienced a local failure as a component of first failure with no regional nodal failures reported [73]. The inclusion of elective nodes in the radiation fields may complicate normal tissue dosimetry, particularly with

respect to small bowel. Representative planning target volumes (PTVs) with and without the inclusion of regional nodes is shown in Figs. 7.1 and 7.2. The inclusion of regional nodes has been shown to compromise the delivery of concurrent full dose systemic therapy [36]. Current trends in management suggest the omission of regional nodes in favor of the delivery of full dose radiosensitizing chemotherapy (i.e., gemcitabine). However, if elective nodal irradiation is performed, a 1 cm radial expansion on the vessel of interest to generate a clinical target volume (CTV) is suggested [74].

If 4D data are available, an internal target volume (ITV) including primary tumor and grossly abnormal regional adenopathy should be contoured on each slice within each phase of the respiratory cycle. A 5 mm radial expansion on ITV is generally appropriate for PTV if daily portal imaging is utilized. ITV to PTV margin should be determined on an institutional basis and may be personalized with the use of gating or breath hold, fiducial placement, and image guided radiotherapy. If 4D data are not available for target delineation, minimum expansions of 2 cm in the superior-inferior plane and 1 cm in the anterior-posterior + medial-lateral planes should be added to GTV to generate a PTV [70].

3D conformal and IMRT planning techniques are reasonably well standardized. For the adjuvant context, planning guidelines have been developed and published based on the current NRG/RTOG protocol [75]. Planning for the unresected patient is facilitated by the in situ presence of the gross tumor volume (GTV) and is readily extended from the adjuvant setting. Once the decision has been made whether the treatment volume is to include nodal volumes or not, then CTV and PTV are readily generated. Ninety-five percent of the PTV should be covered by the prescription dose with heterogeneity limited to <110 % within the PTV. IMRT has been shown to reduce mean dose to the liver, kidneys, stomach, and small bowel, and may allow for dose escalation in the appropriate setting. Based on available data, a dose of 45–50.4 Gy in 25–28 fractions prescribed to the PTV is suggested. More experienced institutions may wish to consider 2.0–2.1 Gy fractions to 50–55 Gy in 25 fractions aimed at tight (CTV based on GTV without including regional nodes) planning volumes. Concurrent radiosensitizing chemotherapy (most commonly gemcitabine or capecitabine) is recommended and prescription dose may vary depending on agents used and their dose intensity.

Organs at risk (including kidneys, stomach, duodenum, spinal cord, liver, small bowel, and large bowel) should be contoured on each planning CT. Planning constraints from the NCCN [76] or from NRG/RTOG 0848 [75] may be utilized. The NCCN guidelines include the following (in 1.8–2.0 Gy/fraction): liver mean dose <30 Gy, spinal cord maximum dose ≤45 Gy, duodenum and small bowel maximum dose ≤55 Gy and no more than 30 % receiving >45 Gy, and no more than 30 % of the total volume of either (baseline functional) kidney ≥18 Gy. Considerations for SBRT planning are considered elsewhere [77–81].

Future Directions

Despite advances in increasing resectability using novel neoadjuvant chemotherapeutic approaches in conjunction with radiotherapy, the predominant pattern of failure after R0 resection remains distant failure. As such, emerging data for the treatment of advanced and metastatic disease will undoubtedly have a profound impact on future directions for the neoadjuvant treatment of borderline resectable pancreatic cancer. A seminal trial reported by Conroy et al. in 2011 [82] showed the superiority of FOLFIRNOX over gemcitabine in the first line treatment of patients with metastatic pancreatic cancer and good performance status. A similarly pivotal trial reported by Van Hoff et al. in 2013 [83] showed the superiority of the addition of nab-paclitaxel to gemcitabine monotherapy. The recently reported results of the SCALOP trial demonstrated that capecitabine-based chemoradiotherapy may be better tolerated than gemcitabine-based chemoradiotherapy [84].

Based on the results of the Conroy and SCALOP trials, an Intergroup pilot study evaluating a strategy of neoadjuvant FOLFIRINOX and capecitabine-based radiation was conducted and recently closed to enrollment (Alliance A021101). In this study, patients with borderline resectable pancreatic cancer received neoadjuvant FOLFIRINOX and capecitabine-based chemoradiotherapy followed by resection and adjuvant gemcitabine. A similar phase II trial (NCT01897454) is currently accruing. In this trial, patients with borderline resectable pancreatic cancer receive FOLFIRINOX followed by gemcitabine-based chemoradiotherapy followed by evaluation for resection. A retrospective analysis of 18 patients with borderline resectable and locally advanced pancreatic cancer suggests that patients who do not convert to radiographic resectability after six cycles of FOLFIRNOX may benefit from chemoradiotherapy [85].

Based on promising results from the recently reported phase I/II short course proton trial and in conjunction with the Von Hoff data, investigators at Massachusetts General Hospital plan to launch a phase III trial in which patients with localized pancreatic cancer will be randomized to receive FOLFIRINOX vs. gemcitabine/nab-paclitaxel followed by short course proton based chemoradiotherapy prior to surgical resection [42].

In Europe, ESPAC-5, a phase II randomized trial for patients with borderline resectable pancreatic cancer, is now accruing. In this trial (with a targeted accrual of 100 patients), patients will be randomized to receive chemotherapy (gemcitabine/capecitabine vs. FOLFIRNOX), chemoradiotherapy (50.4 Gy in 28 fractions with Capecitabine 830 mg/m^2 BID), or upfront surgery. All patients receive adjuvant chemotherapy after surgery, if performed. Patients randomized to chemoradiotherapy do not receive induction chemotherapy.

Summary and Conclusions

Borderline resectable pancreatic cancer was previously an ambiguous diagnosis because of inconsistent definitions and limited imaging technologies. Thus, the interpretation of historical data pertaining to the treatment of patients with borderline resectable pancreatic cancer is confounded by these realities. Current results reflect consensus regarding definitions of resectability and borderline resectability as well as improvements in systemic therapy, surgical morbidity/mortality, and conformal radiotherapy. With these the possibility for resection with curative intent for the borderline resectable patient is

Table 7.4 Selected recent retrospective series on neoadjuvant chemoradiotherapy for borderline resectable pancreatic cancer

References	Resectability criteria	Patients with BRPC	Pre-op regimen	Resection rate (%)	R0 resection rate (of patients resected) (%)	OS in patients with resected BRPC
Stokes et al. [88]	MD Anderson	34	Cape + RT (5050.4 Gy)	45	75	23 months
Katz et al. [33]	MD Anderson	84	Various[a]	38	97	40 months
Patel et al. [93]	NCCN	17	Gem → 5FU + RT (median 50 Gy)	64	89	NR
Takahashi et al. [38]	MD Anderson	80	Gem + RT (50 Gy)	54	98	NR[b]
Kharofaet al. [73]	NCCN[c]	39	Various ctx → gem or cape + RT (50.4 Gy)	56	98	26 months[d]

Cape capecitabine, *Gem* gemcitabine, *5FU* 5-fluorouracil
[a]Includes some patients who received neoadjuvant chemotherapy without radiotherapy (30–50 Gy)
[b]Five-year overall survival 34 %
[c]Modified NCCN criteria defined per institutional protocol
[d]Includes patients with resectable disease at presentation

greater than 75 % and such resections (usually R0 resections) are associated with a greater than 2-year median survival (Table 7.4). The goal of neoadjuvant radiotherapy is to increase resectability as an R0 resection is the only opportunity for potentially curative surgery. The delivery of neoadjuvant radiotherapy should not delay or prevent the delivery of highly active systemic therapy as the predominant cause of death after curative intent resection is distant metastatic progression. As such, an approach involving neoadjuvant chemotherapy followed by chemoradiotherapy (with active concurrent systemic therapy) is favored prior to attempted resection. SBRT and proton beam radiotherapy appear to be viable alternatives to conventionally fractionated neoadjuvant radiotherapy and may allow for the appropriate integration of aggressive chemotherapeutic regimens prior to resection. In all cases, enrollment in clinical trials is highly encouraged for all patients with borderline resectable disease.

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8 Stereotactic Body Radiation Therapy as an Emerging Option for Localized Pancreatic Cancer

Rachit Kumar, Lauren M. Rosati, and Joseph M. Herman

Introduction

Despite improvements in imaging, treatment, and symptom management, the prognosis of a patient with newly diagnosed pancreatic cancer remains exceedingly poor. In 2015, it is estimated that 40,560 of the 48,960 patients diagnosed with pancreatic cancer will die as a consequence of the disease [1]. This translates to an 83 % mortality rate. Pancreatic cancer is the fourth most common cause of cancer-related death among both men and women in the United States [1]. At this time, no prospectively validated screening tool is available, though the incidence of this disease continues to rise.

The majority of patients who present with localized—borderline resectable (BRPC) and locally advanced (LAPC) tumors—disease are unable to undergo a curative resection due to extensive tumor involvement of adjacent vasculature. In these patients, the options for potentially curative therapy include concurrent chemoradiation (CRT), aggressive multi-agent chemotherapy, or chemotherapy followed by CRT [2]. While standard fraction radiation has been considered the standard-of-care in both BRPC and LAPC patients for decades, more recent data has questioned the impact of conventional three-dimensional conformal radiation therapy (3D-CRT) on overall survival, and a significant debate in the field of gastrointestinal oncology has resulted [3–5].

Advanced imaging and radiation techniques allow for an increase in the precision of radiation delivery. The field of radiation oncology has witnessed a paradigm shift in the delivery of radiotherapy from small daily fractions of radiation (1.8–2.5 Gy/day) to large daily doses given over fewer consecutive days or alternating days (5–40 Gy/day) [6]. This radiotherapy technique, entitled stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), is now gaining traction in pancreatic cancer as an option for patients with borderline resectable and locally advanced disease. By delivering a higher daily dose per fraction of radiation over a shorter total number of days, this treatment appears to result in an increased biologically effective dose (BED) as compared to standard radiation [7]. In doing so, a higher level of tumor sterilization and improved clinical and pathologic outcomes may be achieved.

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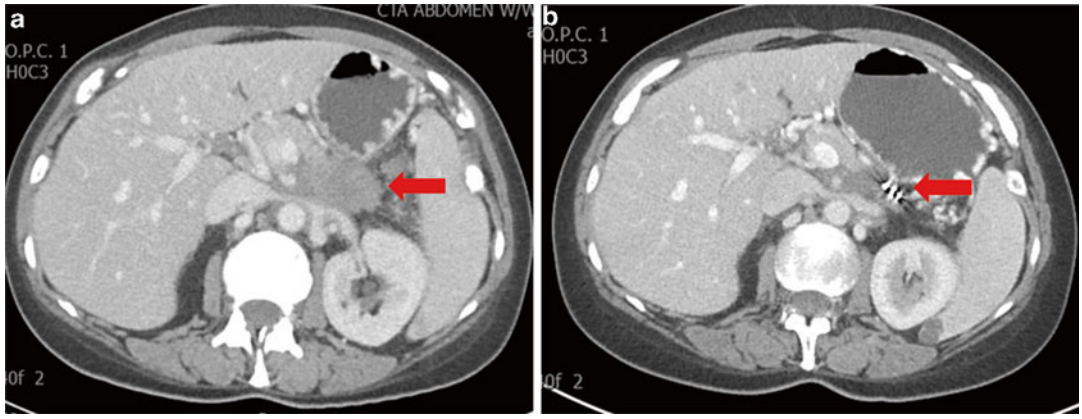

Fig. 8.1 Computed tomography scan of a locally advanced tumor (**a**) prior to chemotherapy and (**b**) following chemotherapy and SBRT to 33 Gy in 5 fractions. Patient then underwent a successful margin- and node-negative resection in which only scattered microscopic foci of adenocarcinoma (a near-pathologic complete response) was found

This can be seen in Fig. 8.1, which provides anecdotal radiographic evidence of the marked response observed after a patient received FOLFIRINOX (5-fluorouracil, irinotecan, leucovorin, and oxaliplatin) chemotherapy and SBRT.

In this chapter, we will explore the published data, including that of retrospective and prospective studies in the field of SBRT for pancreatic cancer. The opportunities and challenges in the utilization of this technique, including appropriate patient selection and treatment methodology, will be discussed.

Resectability in Borderline Resectable and Locally Advanced Pancreatic Cancer

In pancreatic cancer, surgical resectability is considered paramount in achieving a cure. To determine whether a tumor is resectable, careful consideration of arterial and venous involvement—the superior mesenteric artery (SMA), celiac axis, common hepatic artery (CHA), superior mesenteric vein (SMV), and portal vein (PV) specifically—is taken into account. While the nomenclature defining surgical resectability has remained fairly constant for years, the definition of borderline resectable disease was recently formalized by a consensus group from the Americas Hepato-Pancreatico-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), and Society for Surgery of the Alimentary Tract (SSAT) [8]. These criteria are often referred to as the Consensus or Callery guidelines and have been reproduced in Table 8.1. The criteria adopted by the National Comprehensive Cancer Network (NCCN) are listed in Table 8.2 [2]. A more refined definition of borderline resectable tumors, classically a difficult subgroup to define, is noted in Table 8.3 [9]. The definition listed in Table 8.3 provides specific criteria used in the Intergroup trial (A021101) testing neoadjuvant FOLFIRINOX followed by 50.4 Gy of external beam radiation and capecitabine in patients with borderline resectable pancreatic cancer [9]. Due to the heterogeneous definitions of resectability, careful consideration of these criteria and the involved vasculature is necessary to compare clinical outcomes among populations involving patients with borderline resectable and locally advanced pancreatic cancer. Standardization of resectability in pancreatic cancer is essential.

In general, patients with LAPC are considered unsuitable candidates for upfront surgery, in part due to the morbidity and mortality risk associated with vasculature resection [10]. Additionally, the decision to resect a tumor with a high likelihood of a positive margin at the site of vascular involvement is suboptimal as the survival of patients

Table 8.1 The AHPBA/SSO/SSAT pretreatment staging system of pancreatic adenocarcinoma [8]

Resectability status	Criteria	Median survival
Resectable	No distant metastases	20–24 months
	No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or encasement	
	Clear fat planes around the celiac axis, hepatic artery, and SMA	
Borderline resectable	No distant metastases	Resected: ~20 months
	Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction	
	GDA encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis	Unresected: ~11 months
	Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall	
Locally advanced	*HEAD*: No distant metastases; SMA encasement exceeding >180° or any celiac axis abutment; unreconstructible SMA/portal vein occlusion/encasement; extensive hepatic artery involvement; aortic invasion or encasement	9–15 months
	BODY: No distant metastases; SMA or celiac axis encasement >180°; unreconstructible SMV/portal occlusion; aortic invasion	
	TAIL: No distant metastases; SMA or celiac axis encasement >180°	
	ALL: Metastases to lymph node beyond the field of resection	
Metastatic	Any presence of distant metastases	4–6 months

SMV superior mesenteric vein, *SMA* superior mesenteric artery, *GDA* gastroduodenal artery

with a microscopically (R1) or grossly (R2) positive margin has been shown to be significantly inferior to patients resected to a negative (R0) margin [10, 11]. The standard-of-care in these patients is most often upfront chemotherapy alone or CRT. The goal of this therapy is to optimally downsize (or, if possible, sterilize) the tumor to allow for surgical resection and increase the likelihood of improved pathologic outcomes (i.e., margin- and node-negative resection, pathologic complete response). In fact, a recent study has suggested promising outcomes in 40 patients with BRPC or LAPC who underwent neoadjuvant FOLFIRINOX (5-fluorouracil, irinotecan, leucovorin, and oxaliplatin) therapy. Of these 40 patients, 30 (75 %) received radiation therapy: 24 received 50.4 Gy CRT and 5-fluorouracil (5-FU), 10 of which also received a 7–12 Gy intraoperative radiation therapy (IORT) boost, and 6 received proton beam therapy with charged particles. On final pathology, the patients who received neoadjuvant therapy had a significant decrease in lymph node positivity (35 % vs. 79 %) and perineural invasion (72 % vs. 95 %) in

Table 8.2 The NCCN guidelines for pancreatic cancer staging [2]

Stage	Arterial	Venous
Resectable	Clear fat planes around celiac axis, superior mesenteric artery, and hepatic artery	No superior mesenteric vein/portal vein distortion
Borderline resectable	Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis. Tumor abutment of the superior mesenteric artery not to exceed greater than 180°	Venous involvement of the superior mesenteric vein or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and placement
Unresectable	Aortic invasion or encasement. Based on tumor location: pancreatic head—more 180° encasement, any celiac axis abutment, inferior vena cava; pancreatic body/tail—superior mesenteric artery or celiac axis encasement greater than 180°	Unreconstructable superior mesenteric vein/portal vein occlusion

Table 8.3 The Intergroup trial [9] definition of borderline resectable pancreatic cancer

Vessel	Tumor involvement
Superior mesenteric vein–portal vein	Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall, and/or reconstructable occlusion
Superior mesenteric artery	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall
Common hepatic artery	Reconstructable, short-segment interface between tumor and vessel of any degree
Celiac trunk	Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall

comparison with 87 patients who underwent upfront surgery. Furthermore, the neoadjuvant patients achieved margin-negative and node-negative resection rates of 92 % and 65 %, respectively.

Unpublished data exploring neoadjuvant SBRT in borderline and locally advanced patients at Johns Hopkins University. Among 80 resected patients with BRPC or LAPC, 33 received neoadjuvant chemotherapy alone and 47 received induction chemotherapy followed by SBRT. FOLFIRINOX-based chemotherapy was administered to 63 and 45 % of the SBRT group and chemotherapy group, respectively. The majority (57 %) of SBRT patients were deemed unresectable while only 24 % in the chemotherapy alone group had LAPC ($p=0.009$). Pancreaticoduodenectomy was performed in 68 % of patients who underwent SBRT vs. 85 % of patients who received chemotherapy ($p=$NS). In the SBRT group, the R0 resection rate was 85 % in BRPC and 89 % in LAPC vs. 48 % in BRPC and 63 % in LAPC patients in the chemotherapy group ($p=$NS). Node-negative resections were achieved in 72 % of patients who received SBRT (60 % in BRPC, 81 % in LAPC) vs. 42 % of patients who received chemotherapy alone (40 % in BRPC, 50 % in LAPC) ($p=$NS). The pathologic complete response rate was 13 % in the SBRT group (10 % in BRPC, 15 % in LAPC) vs. 3 % in the chemo group (0 % in BRPC, 13 % in LAPC) ($p=$NS). The near-pathologic complete response rate, defined as microscopic foci of single cells or groups of single cells of adenocarcinoma, was 28 % in the SBRT group (25 % in BRPC, 30 % in LAPC) vs. 12 % in the chemotherapy group (12 % in BRPC, 13 % in LAPC) ($p=$NS). Figures 8.2 and 8.3 demonstrate the extensive treatment effect seen macroscopically (Fig. 8.2) and microscopically (Fig. 8.3) in patients who underwent neoadjuvant SBRT. Further follow-up data is underway to

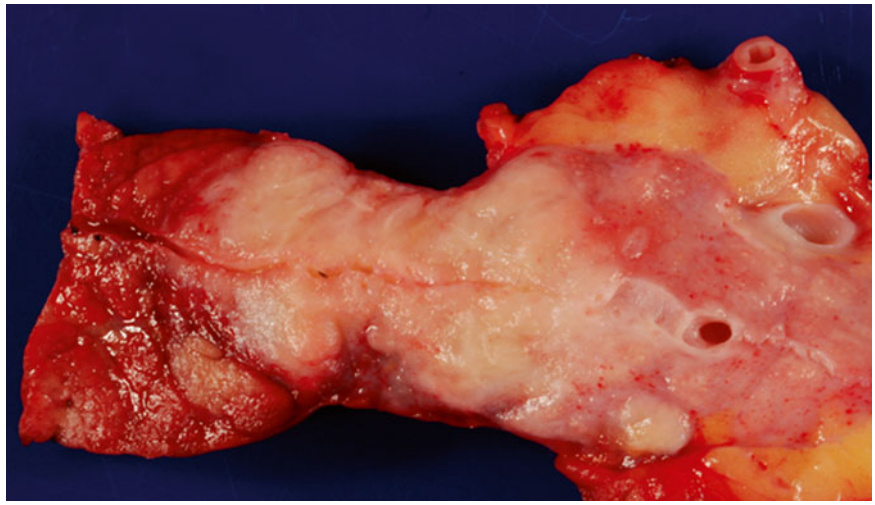

Fig. 8.2 Resected bivalve specimen has been sliced along the pancreatic duct. The pancreas (*the left side*) looks hyperemic. The tumor is located in the center. The upstream pancreas is to the *right* (towards the spleen). The dilated pancreatic duct and the stroma appear to be edematous. *Courtesy of Ralph H. Hruban*

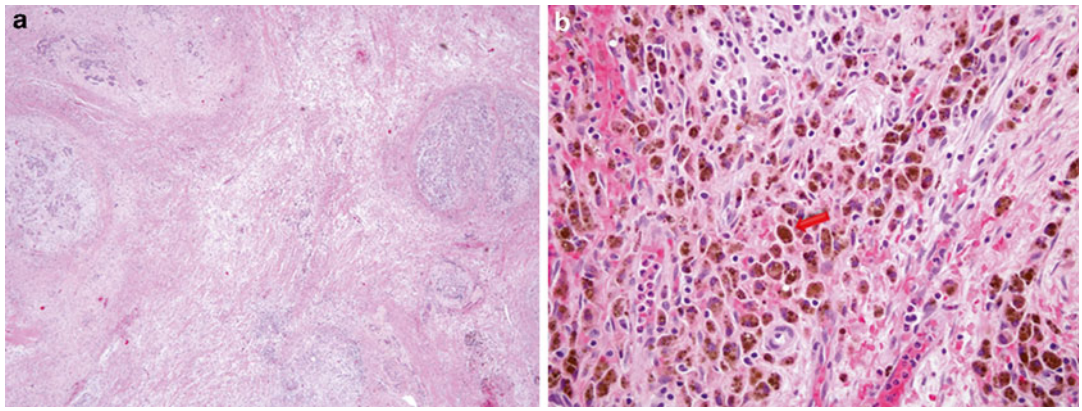

Fig. 8.3 Microscopic evidence of (**a**) extensive treatment effect observed following pancreas SBRT to a tumor that was measured to be 3.8 cm in size, and (**b**) the presence of hemosiderin-laden macrophages (*brown* cells), inflammatory cells that are suggestive of a reactive process following therapy

determine the impact of these pathologic outcomes on survival.

Standard Treatment for Borderline Resectable and Locally Advanced Pancreatic Cancer

The morbidity and potential mortality associated with surgical resection of BRPC and LAPC implies that CRT or chemotherapy alone is the only viable option for cure in these patients [12]. Despite the completion of multiple studies on this topic, no consensus regarding the optimal course of management exists. The most recent NCCN clinical practice guidelines recommend enrollment onto a clinical trial as the first-line option [2]. In patients with good performance status, multi-agent chemotherapy followed by CRT is considered appropriate.

Data supporting the above approach are derived from decades of clinical trials dating back to the 1980s [4, 5, 13–17]. Table 8.4 presents a selection of the clinical trials which have

Table 8.4 Selected studies of locally advanced pancreatic cancer

Study	Number	Treatments	Median survival (months)	*P* value
GITSG Moertel [13]	194	60 Gy vs. 60 Gy + 5FU (bolus) or 40 Gy + 5FU (B)	5.7 vs. 10.1 or 10.6	<0.01
GITSG [14]	43	Streptozocin, MMC, 5FU vs. 54Gy + 5FU (bolus) → Streptozocin, MMC, 5FU	8 vs. 10.5	<0.02
ECOG Klaassen [15]	91	5FU (bolus) vs. 40 Gy + 5FU (bolus) → 5FU	8.2 vs. 8.3	ns
FFCD/SFRO Chauffert [5]	119	Gem vs. 60 Gy + 5FU (continuous infusion) + Cis → Gem	13 vs. 8.6	0.03
ECOG Loehrer [4]	74	Gem vs. 50.4 Gy + Gem → Gem	9.2 vs. 11	0.04
GERCOR Huguet [16][a]	181	Gem-based Chemo vs. Gem-based Chemo → Chemorad	1.7 vs. 15	0.0009
MDACC Krishnan [17][a]	323	Chemorad vs. Gem-based Chemo → Chemorad	8.5 vs. 11.9	<0.001

5FU 5-fluorouracil, *MMC* mitomycin-C, *Gem* gemcitabine, *Cis* cisplatin, *Chemo* chemotherapy, *Chemorad* radiation in concurrence with 5FU, Gem, or capecitabine
[a]Retrospective studies

investigated the role of standard fractionated radiation in LAPC. As is evidenced by the table, the survival of patients has not progressed dramatically despite the numerous advances in chemotherapy agents and radiation technology in the last three decades.

The most significant debate in the appropriate management of patients with BRPC and LAPC centers on the role of radiation in this disease. Some studies have demonstrated a survival decrement with the application of radiation therapy in this patient population. However, these studies suffer from major drawbacks, including poor radiation quality assurance, excess radiation dose, unclear dose constraints for adjacent critical structures, and the use of "split-course" radiation in which a 2-week treatment break is part of the planned course of treatment. Other studies have shown a potential benefit for radiotherapy [4]. However, a major criticism of all these data is the utilization of outdated or ineffective chemotherapy.

A more modern approach to the treatment of this disease has been to use combination chemotherapy with either FOLFIRINOX or gemcitabine with nab-paclitaxel [18–20]. These two combination chemotherapeutic regimens have demonstrated a survival benefit in comparison to gemcitabine alone, albeit in the metastatic setting. In BRPC and LAPC, the current NCCN guidelines recommend either single-agent gemcitabine or combination chemotherapy, with CRT preferred following a course of initial chemotherapy. SBRT is listed as an option, though its use is encouraged as part of enrollment on a clinical trial [2].

Stereotactic Body Radiation Therapy

Traditional radiotherapy has been delivered in small daily fractions to take advantage of the ability of normal human tissue to repair radiation more quickly than tumor tissue. This "therapeutic window" is particularly critical in anatomical locations prone to severe, irreparable radiation damage [7]. One of the dangers of using high-dose-per-fraction radiation is the risk of over-

whelming the therapeutic window and damaging sensitive adjacent normal tissues without precise targeting of the tumor [21, 22]. However, the development of advanced radiotherapy techniques in the last two decades has dramatically changed the landscape of radiation oncology [6].

SBRT is defined as the use of intensity modulation, image guidance, tumor motion control, and stereotactic targeting to deliver a high dose of radiation to the tumor in five or less fractions [6]. Each of the aforementioned techniques and technological developments contributed to the ability to use this type of treatment. Image guidance ensures that the tumor and/or fiducial or stent is visualized at the time of each treatment, allowing for reduced treatment margins (thereby reducing normal tissue exposure). Whereas treatment margins had historically been measured in centimeters, the use of this technology has reduced these margins to only a few millimeters (mm) [6].

SBRT was first used to treat intracranial neoplasms [23]. Later, this was expanded to extracranial sites, particularly with early stage lung cancer, demonstrating outstanding local control, virtually absent acute (<3 months) toxicity, and minimal chronic (>3 months) toxicity [24]. By nature of its "parallel" normal tissue unit arrangement, lung tissue benefits from being able to receive an ablative dose to one region without compromising the overall function of the organ. In contrast, the perceived risk of using SBRT in locations abutting normal tissues with a "serial" arrangement of normal tissues, including the small bowel and stomach as seen with the pancreas, is more concerning. Consequently, SBRT to areas within the abdomen and pelvis have been adopted with much more caution [6]. Without a firm understanding of the dose constraints of these sensitive organs at risk (OARs), practitioners have been hesitant to use ablative doses of radiation in this region. As data has emerged from groups that have utilized this approach, a stronger understanding of the dose tolerance of the small bowel and stomach has led to the widespread adoption of SBRT in the infradiaphragmatic space [25]. An analysis of patterns of care of radiation delivery from 39 centers in the United States indicates that the use of SBRT for pancreatic cancer is increasing, but still represents a relatively small absolute value [25].

In the following sections, the clinical results, toxicities, and techniques for the safe and effective utilization of pancreas SBRT are described.

Clinical Trials Utilizing SBRT for Borderline Resectable and Locally Advanced Pancreatic Cancer

In the last decade, retrospective reports and prospective clinical trials have supported the use of pancreas SBRT as a potent method for providing excellent tumor control, increasing resectability rates, and improving surgical outcomes in patients with BRPC and LAPC (Table 8.5) [26–40]. However, heterogeneity in selection criteria, patient immobilization technique, radiation dose, radiation planning techniques, and radiation delivery devices limit direct comparisons between these studies.

The first published data using SBRT in pancreatic cancer was from researchers at Stanford University [26]. Koong and colleagues described their experience treating 15 patients with LAPC using a CyberKnife (Accuray Inc, Sunnyvale, CA, USA) linear accelerator. Two patients had previously received conventionally fractionated radiation to a dose of 50 Gy. This phase I dose escalation study planned to increase radiation dose from 15 to 25 Gy in a single fraction if patients met predefined toxicity criteria at 12 weeks. Three patients were treated at 15 Gy in one fraction, five patients at 20 Gy in one fraction, and seven patients at 25 Gy in one fraction. Even at the highest dose level, no grade 3 or greater acute toxicity was observed. With a median follow-up of 5 months, no local failures were observed, though this may be a consequence of the short median follow-up interval. The median survival noted in the study was 11 months and, in that time, only acute grade 2 or less toxicity was observed.

Shortly thereafter, researchers from Aarhus University in Denmark published their experience with linear accelerator (Linac)-based SBRT

Table 8.5 Prospective and retrospective investigations in stereotactic radiotherapy for pancreatic cancer

Author	Prosp	Retro	BR	LA	Total	LINAC/CK	DPF (Gy)	Fractions	Total dose (Gy)	1 year LC	PFS (months)	OS (months)	1 year OS	2 year OS
Koong [26]	I		0	15	15	CK	15–25	1	15–25	100 %		11		
Hoyer [27]	I		0	22	22	LINAC	15	3	45	57 %	4.8	5.4	5 %	
Koong [28]	I/II		0	16	16	CK	25	1	25	94 %	4	11.4	15 %	
Chang [29]		X	0	45	77	CK	25	1	25	87 %	26 % @ 6 months	11.9	21 %	
Polistina [30]	I		0	23	23	CK	10	3	30	83 %	7.3	10.6	39 %	0 %
Schellenberg [31]	II		0	20	20	CK	25	1	25	75 %	9.2	11.8	50 %	20 %
Mahadevan [32]		X	0	36	36	CK	8–12	3	24–36	78 %	9.6	14.3		
Mahadevan [33]		X	0	47	47	CK	8–12	3	24–36	85 %	15	20		
Chuong [34]		X	57	16	73	LINAC	7–10	5	35–50	86 %	9.7 BR/ 9.8 LA	16.4/15	72.2/68.1	
Tozzi [35]	I/II		21 LA, 9 recurrent		30	LINAC	7.5	6	45	85 %	8	11	47 %	
Kim [36]		X	10	7	17	LINAC	8–24	1–3	24–36	53 %	6.3	7.6[a]	35 %	
Rajagopalan [37]		X	7	5	12	both	10–24	1–3	25–36		6.3	10.9	92 %	64 %
Gurka [38]		X	6	28	34	CK	5–6	5	25–30	79 %	6.8	12.3[a]		
Moningi [39]		X	14	74	88	LINAC	5–6.6	5	25–33	LPFS 13.9	9.8	18.4		
Herman [40]	II		0	49	49	both	6.6	5	33	78 %	7.8	13.9	59 %	18 %

Prosp prospective study, *Retro* retrospective study, *BR* borderline resectable, *LA* locally advanced, *LINAC* linear accelerator, *CK* CyberKnife ®; *LC* local control, *PFS*, progression-free survival, *OS* overall survival, *LPFS* local progression-free survival

[a]Indicates that survival was calculated from the end of SBRT (otherwise noted from date of diagnosis)

[27]. Their phase I trial used three fractions of 15 Gy each in 22 patients with LAPC. The results of this trial were significantly inferior to the local control rate and overall survival seen in the aforementioned Stanford study. Local control was only achieved in 57 % of patients, and median overall survival was 5.4 months (vs. 11 months in the Stanford study). Finally, when assessing patient tolerability of this regimen, a much higher toxicity rate was seen, with 79 % of patients experiencing a grade 2 or greater toxicity.

Considering the starkly different results for both trials using the same disease and treatment, a comparison of the treatment technique in both sets of clinical trials must be performed. In the 2004 Stanford study, the breath-hold technique was used to account for tumor motion during respiration. Each dose of radiation was delivered during deep inspiration only, allowing for small tumor margins of 2.5 mm [26]. However, in the 2005 Aarhus analysis, abdominal compression was utilized, and the tumor margins were much larger: 10 mm in the cranio-caudal dimension and 5 mm in the transverse dimension [27]. Additionally, whereas implanted fiducials within the tumor were used to target the lesion during treatment in the Stanford trial, this was not performed in the Aarhus trial [26, 27]. Based on interpretation of these two sets of data, the recommendation for the implementation of SBRT in pancreatic cancer has been to use both tumor motion management strategies as well as image guidance to optimally target the lesion and limit margins to <5 mm. This has limited untoward treatment-related toxicity and improved oncologic outcomes.

The largest prospective experience in pancreas SBRT has recently been published [40]. This multi-institutional phase II trial included patients treated at three major academic centers and accrued 49 LAPC patients. All patients were allowed up to 3 doses of gemcitabine (to allow time for SBRT simulation and planning), followed by a five-fraction SBRT regimen to a total cumulative dose of 33 Gy (6.6 Gy per fraction) delivered over a maximum of 2 weeks. While direct comparison to prior trials can be challenging, the median overall survival of 13.9 months seen in this trial is superior to other published studies. Despite including only patients with LAPC, 18 % of patients survived 2 years or longer from the date of diagnosis. The local control rate was equally impressive; the 1-year freedom from local progression was 78 %.

A large retrospective series of patients treated with pancreas SBRT has been published by investigators from Johns Hopkins University [39]. Eighty-eight patients with both BRPC and LAPC were treated with five-fraction SBRT treated to a total dose of 33 Gy. Of these 88 patients, 14 had BRPC and 74 had LAPC, and 32 (80 %) of the 74 patients with LAPC were treated on the aforementioned multi-institutional clinical trial. All patients had an ECOG performance status of 0 or 1. Prior to radiation, the vast majority of patients were treated with gemcitabine-based or FOLFIRINOX chemotherapy. Survival from diagnosis for the entire cohort was 18.4 months, specifically 18.4 months for patients with LAPC and 14.4 months for patients with BRPC. As with the multi-institutional trial, SBRT appeared to significantly improve local control, with median local progression-free survival found to be 13.9 months. However, the overall progression-free survival in this study was 9.8 months, demonstrating that distant failure continues to be a major detriment in this patient population.

A decade worth of published data demonstrates that SBRT in BRPC and LAPC is effective in providing local tumor control, and in some cases, significant patient longevity. However, the matter of patient safety remains critical in deciding whether or not this treatment is appropriate to supplant the role of standard dose and fractionation radiation.

Stereotactic Body Radiation Therapy and Treatment-Related Toxicity

To determine the safety profile of SBRT in pancreatic cancer, the most severe toxicities from the published studies should be analyzed.

Standard radiotherapy for pancreatic cancer, in which up to 6 weeks of daily fractionated radiation are delivered, is accompanied by fairly significant toxicity, most commonly gastrointestinal and hematologic, throughout the duration of treatment [4]. Indeed, early radiotherapy trials that demon-

strated inferior outcomes with the application of adjuvant radiation included a mandatory 2-week treatment break due to known treatment toxicity [41]. Due to the exquisite radiosensitivity of the gastrointestinal tract, the proximity of the stomach, small bowel, and large bowel presents a significant challenge for delivering radiation in the acute setting. However, fractionated treatment maintains the integrity of the gastrointestinal tract by limiting the dose to critical structures below an established threshold. Chronic devastating toxicity, including gastrointestinal obstruction, ulcer, and perforation, may generally be avoided with fractionation.

While SBRT may allow for limited acute toxicity due to the completion of radiation within 3–5 treatments, the initial concerns from the greater radiation oncology community have been the risk of potentially lethal late toxicities resulting from a higher BED to sensitive gastrointestinal structures [21, 22]. However, the published data demonstrate that, by and large, SBRT can be completed with minimal acute and late toxicity when performed with appropriate patient selection, tumor motion control, image guidance, and well-defined dose constraints [26–40]. As previously discussed, abdominal SBRT is imprecise and potentially destructive without tumor motion management and image guidance [26, 27].

To understand the risk of toxicity from this type of treatment, a comparison may be made between two different SBRT regimens from separate institutions. Investigators from Harvard University have published their results using a three-fraction SBRT regimen treating up to a total dose of 36 Gy ($BED_{10\,Gy}$ = 79 Gy, $BED_{3\,Gy}$ = 180 Gy) [33]. While a significant number of patients had acute grade 1 (56 % fatigue, 18 % nausea) and grade 2 (23 % nausea) toxicity, no acute grade 3 or greater toxicity was seen. Further, the rate of late grade 3 or greater toxicity was also low, noted in only 6 % of patients (two patients with gastrointestinal hemorrhage requiring endoscopic intervention and transfusion, one patient with gastric outlet obstruction). Motion management was achieved using implanted fiducials within the tumor thereby allowing for tumor tracking using the CyberKnife Synchrony system (Accuray Inc., Sunnyvale, CA).

Investigators from Johns Hopkins University have utilized a five-fraction SBRT regimen treated up to a total dose of 33 Gy ($BED_{10\,Gy}$ = 54 Gy, $BED_{3\,Gy}$ = 103 Gy) [39]. Acute toxicity was found to be fairly minimal, with the two most common grade 2 toxicities reported as lymphopenia (14.7 % of patients) and fatigue (8.0 %). Acute grade 3 or greater gastrointestinal toxicities occurred in 3.4 % of patients. Late grade 3 or greater toxicity occurred in five patients (5.7 %): three duodenal ulcers (grade 3), one enteric fistula (grade 4), and one gastrointestinal hemorrhage (grade 5). The late grade 5 toxicity occurred in a patient with tumor invasion into the duodenal wall. Following tumor regression after treatment with SBRT, an ulcer resulted and, after a biliary stent exchange, he possibly had a perforation that resulted in a fatal gastrointestinal hemorrhage less than a day later. Because these events were a possible late toxicity due to the SBRT, the investigators adjusted their patient enrollment criteria to ensure that any patient with direct tumor invasion into the lumen of the stomach or duodenum on endoscopic ultrasound is ineligible for SBRT. Treatment planning on this protocol included a pretreatment endoscopic ultrasound with the implantation of gold fiducials to identify the lesion, a breath-hold technique to prevent tumor motion, and daily cone-beam computed tomography to accurately track the lesion during treatment.

Despite using a higher BED of radiation, the above data support the safety of SBRT in BRPC and LAPC when using appropriate tumor localization, motion management, and daily imaging. It is anticipated that long-term data and a comparison between standard radiation and dose-escalated SBRT will be forthcoming from the Alliance for Clinical Trials in Oncology three-arm clinical trial that is currently being developed to investigate the role of neoadjuvant chemotherapy vs. chemoradiation vs. chemotherapy and SBRT.

Impact of Stereotactic Body Radiation Therapy on Quality of Life and Pain

Even in pancreatic cancer patients who respond well to the most aggressive therapies, life expectancy is limited and maximizing quality of life and ameliorating pain is imperative. In addition

to physician assessment of patient toxicity, several validated metrics have been used to assess patient-reported outcomes such as quality of life and symptom burden. Most frequently employed are the European Organization for Research and Treatment in Cancer quality of life core cancer questionnaire (EORTC QLQ-C30) and pancreatic cancer-specific module (EORTC QLQ-PAN26) [42, 43]. Although quality of life data are scarce, there have been a few published reports that explore these outcomes.

A number of studies have used these questionnaires in the setting of standard CRT in BRPC and LAPC [44, 45]. Serrano and colleagues reported a decline in global quality of life after neoadjuvant standard CRT and one cycle of chemotherapy in BRPC and resectable patients, whereas additional studies demonstrated unchanged or improved global quality of life at 3–4 month post-CRT follow-up when compared to baseline [45, 46]. Improvement in pain and jaundice after completion of CRT was reported; however, patients also experienced deterioration in physical and social functioning, an increase in diarrhea, nausea, and vomiting, and a variable impact on appetite change.

The previously mentioned prospective SBRT study indicated unchanged global quality of life scores from baseline to 4 weeks after SBRT and 4 months after SBRT [40]. Furthermore, patients demonstrated a significant improvement in pancreatic pain, body image, and jaundice scores on the QLQ-PAN26 from pre-SBRT values to 4 weeks post-SBRT. From 4 weeks pre-SBRT to 4 months post-SBRT, an improvement in body image approached statistical significance (Rao et al., publication forthcoming). Further prospective evaluation of quality of life data is necessary to assess optimal therapies in localized pancreatic cancer.

Stereotactic Body Radiation Therapy in Patients with Recurrent Pancreatic Cancer

Given the locally aggressive nature of pancreatic cancer, local recurrences may occur even after resection and adjuvant concurrent CRT. Surgical resection in the setting of recurrent disease is often difficult and, even when accomplished, rarely results in disease clearance [47]. In patients previously treated with standard radiation who later suffer local tumor progression, SBRT has been investigated as a viable option to provide local control or to palliate epigastric pain. Limited data exists regarding this patient population, but at least three studies have utilized SBRT in this clinical scenario, and are listed in Table 8.6 [35, 48, 49].

Tozzi and colleagues combined their analysis of patients treated with SBRT in LAPC and the setting of recurrent pancreatic disease [35]. Their analysis did not separate these two entities, but they specifically noted that the local control outcome in patients treated in the recurrent setting and LAPC were equivalent when using a dose of 45 Gy in six fractions (76 % at 2 years).

Lominska et al. and Wild et al. have published their individual institutional results in patients treated with SBRT for recurrent disease following standard CRT [48, 49]. Lominska and colleagues reported their results on the treatment of 28 patients treated with SBRT in the recurrent setting after receiving a median dose of 50.4 Gy of prior external beam radiation [48]. Various treatment fractionation schemes were utilized, most commonly 24 or 21 Gy in three fractions. Median follow-up was expectedly short in this analysis (5.9 months), with 1-year survival noted to be 18 %. Local control, however, was achieved in 86 % of patients. Wild

Table 8.6 Stereotactic radiation in the setting of locally recurrent pancreatic cancer

Author	Number	LINAC/CK	Dose Per Fraction	Fractions	Total dose	1 year LC	PFS	OS	1 Year OS
Tozzi [35]	9	LINAC	7.5	6	45	85 %	8	11	47 %
Wild [49]	18	both	5	5	25		3.7	8.8[a]	
Lominska [48]	14	CK	7 (4–8)	3 (3–5)	22.5 (20–30)	86 %		5.9	18 %

LINAC linear accelerator, *CK* CyberKnife ®, *LC* local control, *PFS* progression-free survival, *OS* overall survival
[a]Indicates that survival was calculated from the end of SBRT (otherwise noted from date of diagnosis)

and colleagues utilized Linac- and CyberKnife-based radiation delivery of SBRT (to a median dose of 25.0 Gy in five fractions) to 18 patients who experienced local progression after adjuvant CRT (15 patients) or definitive CRT (3 patients) to a prior median dose of 50.4 Gy at Stanford or Johns Hopkins University [49]. Median overall survival in this patient population was found to be 8.8 months following SBRT. Furthermore, 57 % of patients with abdominal or back pain prior to SBRT were able to achieve palliation following treatment delivery. The time frame of local recurrence at 9 months was found to be an important delineation in this study. Patients who suffered local recurrence within 9 months following initial surgery or definitive CRT lived only 3.4 months following SBRT, whereas those whose local failure occurred after 9 months lived 11.3 months following SBRT ($p=0.019$). Freedom from local progression was 78 % at 6 months and 62 % at 12 months after completing SBRT, likely reflecting the lower BED of this fractionation. The treatment was safe in both of these studies, with late grade ≥3 toxicity in two patients and one patient, respectively.

In this population with limited treatment options, SBRT represents a reasonable option for safe and effective local tumor control. Although prospective data in this patient population is likely to be limited, enrollment on clinical trials or tumor registries should be encouraged to gather further information and gain long-term efficacy and toxicity data.

Techniques for Implementation of Stereotactic Body Radiation Therapy in Pancreatic Cancer

SBRT trials in pancreatic cancer may vary in the dose utilized, but consistently use multiple measures to ensure patient safety and reproducibility. At all phases of the treatment, from simulation to radiation delivery, accuracy and precision are paramount. The following section represents the authors' consensus on patients treated definitively with pancreas SBRT [34]. Appropriate patient selection is the first step in delivering safe treatment with SBRT. Patients should be in a position to benefit from this more aggressive local treatment, i.e., ideally a performance status of two or better (ECOG ≤2). Specifically, a life expectancy of more than 6 months should be considered minimum, as was noted on the prospective, multi-institutional trial [40]. Tumor size is an additional key criterion, though this varies between studies—most of which involve a tumor under 100 cc, though the largest PTV was noted to be greater than 500 cc [26, 33, 37, 40].

A pre-radiation upper endoscopy procedure should be performed to accurately stage the tumor, to assess tumor extent into the duodenum and/or stomach, and to place gold markers (fiducials) into the lesion for precise tumor localization. We believe there is an increased risk of complications when the tumor directly extends into the stomach or bowel. Consequently, the investigators recommend that SBRT be limited to patients without this adverse finding. Regarding the placement of fiducial markers into the pancreas, one study has explored whether coiled fiducials were superior to traditional, linear fiducials in reducing fiducial migration [50]. The authors found that traditional fiducials had improved visualization compared to coiled fiducials, with no difference in fiducial migration or complications of placement. Traditional, linear fiducials remain the preferred choice for pancreas SBRT at this time.

Patients receiving SBRT for pancreatic cancer should be simulated using a CT scan (3 mm slices) with intravenous and oral contrast (240 cc) to highlight the tumor and standardize gastric filling (give 240 cc of water) during treatment. Many centers utilize positron emission tomography/computed tomography (PET/CT) scans to help identify the lesions as well as monitor for treatment response [51, 52].

As with any site in Radiation Oncology, appropriate immobilization at the time of simulation is paramount in importance. Given the proximity of the pancreas to the diaphragm, tumor motion is common and expected. As previously mentioned, multiple investigators have published their findings on tumor motion and appropriate margins for the use of SBRT in localized pancreatic cancer [53–58]. Table 8.7 lists the movement of pancreas tumors in different planes during the respiratory cycle. This data supports that pancre-

Table 8.7 Pancreatic tumor motion for stereotactic radiation assessed with varying modalities

Author	*N*	Modality	Sup-Inf (mm)	Left-right (mm)	Ant-Post (mm)
Minn [53]	20	FB	0.9–28.8	0.1–13.7	0.2–7.6
		CK	0.5–12.7	0.4–9.4	0.6–5.5
Heinzerling [55]	10	FB	1.2–8.9	1.0–3.8	0.2–2.6
		AC	0.8–5.7	0.1–1.0	0.2–8.9
Knybel [56]	20	FB	4.8–23.4	2.6–6.7	2.9–8.2
Song [54]	16	CK	1.0–4.0	1.0–3.0	5.0–16.0
Wang [57]	11	FB	1.0–15.0	1.0–7.0	0.0–18.0
Goldstein [58]	30	FB	1.2–10.2	0.2–6.7	0.1–7.1

N patient number, *Sup* superior, *Inf* inferior, *Ant* anterior, *Post* posterior, *CK* CyberKnife ®, *FB* free breathing, *AC* abdominal compression

Table 8.8 Recommended dose constraints for five-fraction SBRT

Normal tissue	Recommended constraint (5 fractions)
Proximal small bowel and stomach (within 1 cm of PTV in any plane)	9 cc <15 Gy
	3 cc <20 Gy
	1 cc <33 Gy
Combined kidneys	V75 % < 12 Gy
Spinal cord	1 cc <8 Gy

atic motion is a concern during radiation treatment and should be considered when planning these patients.

Tumor motion is often the greatest in the superior-inferior plane or the anterior-posterior plane, demonstrating the need for careful assessment of this factor at the time of treatment planning. To help stabilize the tumor, some centers utilize abdominal compression in which a device is applied to the abdomen to provide direct anterior pressure, thereby limiting breathing induced abdominal motion. Heinzerling's data supports that this is an adequate method to help reduce tumor motion, thereby increasing reproducibility [55]. Other centers prefer a "breath-hold" technique using active breathing control in which the patient is instructed to pause their respiration at either full inspiration or expiration during which the treatment is delivered [39]. Again, no consensus exists as to whether treatment at full inspiration or expiration is optimal, though a small study (18 patients) from Taniguchi recommends treating patients at full expiration to minimize duodenal toxicity [59]. No data exists to specify which immobilization method is optimal and largely becomes a choice of the treating physician and institution. Lastly, in regard to tumor motion, daily imaging during treatment is a requirement. This can be accomplished using a cone-beam CT scan at the time of treatment, orthogonal kilovoltage (kV) imaging, and/or real-time tumor tracking.

The appropriate dose of radiation in pancreas SBRT is also the subject of significant debate. As noted in Table 8.5, the dose and fractionation has varied from 25 Gy in one fraction to 5 Gy in five fractions. Brunner et al. has completed a review of published data on patients treated with pancreatic SBRT from 2000 to 2013 [60]. By assessing the $BED_{10\,Gy}$ and $BED_{3\,Gy}$, as well as the BED in 2 Gy fractions (EQD2), the authors of this review attempted to estimate the therapeutic window for tumor response and normal tissue complications from different radiation dose regimens. Their results demonstrated that a weak correlation was found between EQD2-α/β10 and BED-α/β10 (tumor control), but a much stronger correlation was found for EQD2-α/β3 and BED-α/β3 (normal tissue toxicity). A 5 and 10 % rate of late grade ≥2 toxicity was seen at EQD2-α/β3 doses of 66 and 100 Gy, respectively. This data is important for helping to determine the optimal dose to avoid long-term complications in these patients, but needs to be further refined. Regardless of the dose that is chosen for treatment, the physician should utilize published dose constraints from institutions utilizing a similar dosing regimen. For reference, dose constraints to surrounding OARs from the recently published multi-institutional trial using 33 Gy in five fractions are presented in Table 8.8 [40]. An SBRT treatment plan can be found in Fig. 8.4.

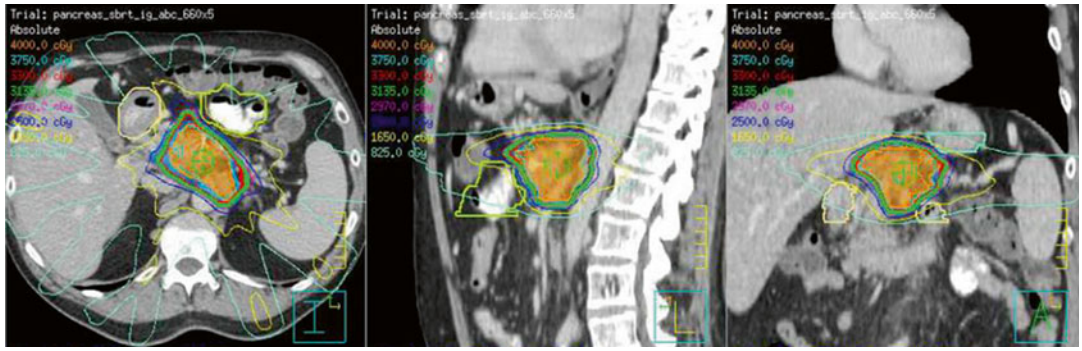

Fig. 8.4 Example of a pancreas SBRT treatment plan. Patient was treated to 33 Gy in 5 fractions (6.6 Gy per fraction). Note that each color represents the isodose distribution of prescription dose. Beyond the isocenter, rapid dose falloff is achieved in order to minimize exposure to surrounding organs at risk such as the stomach and small bowel

Finally, it is important to support patients during and after SBRT. Due to the proximity of the lesions to sensitive gastrointestinal mucosa, prophylactic use of anti-nausea medication is important. The authors of this chapter recommend using ondansetron, with a minimum dose of 8 mg at least 1 h prior to therapy. Likewise, gastrointestinal reflux can be frustrating for patients after treatment, and the use of proton pump inhibitors or H_2-antagonists may also help ameliorate this side effect. These medications may also be prescribed as a prophylactic measure to decrease the risk of developing stomach and/or bowel ulceration. The authors recommend taking a proton pump inhibitor daily during, and ideally 6 months following, the administration of SBRT. Furthermore, pancreatic enzymes are recommended to aid in digestion and absorption of nutrients and reduce the frequency and/or severity of digestive symptoms such as gas, bloating, and loose, oily stools.

Conclusion

The optimal treatment for patients with BRPC and LAPC remains an area of active investigation [61, 62]. Traditional chemotherapy and CRT remains only partially effective in treating this disease and is, at best, a temporizing measure for disease progression. Without the ability to significantly downstage these patients and render their disease resectable, the ability to cure these patients is unlikely. SBRT has demonstrated significantly improved rates of local tumor control, tumor down-staging, treatment response, and resectability rates. While more prospective, randomized data is necessary to officially compare SBRT with standard CRT, the current results with SBRT appear favorable and should be pursued in future clinical trials. Additionally, by reducing the amount of time these patients spend undergoing radiation, the delay in time to the delivery of full-dose chemotherapy is reduced, and the opportunity for both local and distant control is improved. Though the published results of this treatment are still early, they provide a measure of guarded optimism to radiation oncologists treating an otherwise uniformly lethal disease.

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Assessment of Response to Preoperative Therapy

9

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the tenth most common type of cancer in the USA and the UK but accounts for the fourth, respectively, sixth most frequent type of cancer-related death in these countries [1–3]. PDAC has an overall median survival of less than 6 months and one of the lowest overall 5-year survival rates of any malignant disease with 0.4–5 % [4, 5]. Data from the US Surveillance Epidemiology and End Results database indicate that 53 % of all patients with PDAC have concomitant distant metastases at the time of diagnosis, 15–20 % are eligible for potentially curative resection, and roughly 25 % present with locally advanced (LAPC) or borderline (BRPC) disease [6]. Furthermore, 8–15 % of PDAC patients die of locally advanced disease without distant metastases [7].

In this subgroup, patients with BRPC have higher rates of margin-positive resections and local recurrence compared to patients with resectable PDAC. The prognosis of BRPC, however, seems significantly better than that of LAPC, but significantly worse than that of non-locally advanced, resectable patients [8].

In BRPC and LAPC, a number of theoretical benefits for neoadjuvant treatment strategies have been put forward: (a) downsizing of the tumor to increase the rate of microscopic complete resection; (b) downsizing of the tumor to convert unresectable to (borderline) resectable tumors; (c) treatment of occult micrometastases; (d) selecting suitable candidates for surgical resection.

As for other solid tumors, for which neoadjuvant treatment regimens have been well established (e.g., rectal, breast, or gastric cancer), primary staging and restaging after neoadjuvant treatment is an essential component to select suitable patients for preoperative treatment and consequent resection. However, clear definitions of BRPC or LAPC have been lacking in the past, which has hampered the conduct, analysis, and comparability of clinical trials as has been pointed out in Chap. 2 of this book. Similarly, universally acceptable definitions for response assessment following preoperative therapy are lacking. In this chapter, we aim to give an overview of commonly used criteria for response evaluation and point to some inherent pitfalls of these endpoints (Table 9.1).

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Table 9.1 Overview of common response criteria in pancreatic cancer

Response criteria	Groups	Definition	Advantages	Disadvantages	References
Radiologic					
RECIST	Complete response	Disappearance	– Objective, well-evaluated response measure in solid tumors	– Not well established in BRCP and LAPC	[12]
	Partial response	30 % decrease		– Complete response rare in PDAC	
	Stable disease	Neither partial response nor progressive disease criteria met		– Bad correlation with surgical and pathologic endpoints	
	Progressive disease	20 % increase; no complete response, partial response, or stable disease documented before increased disease			
NCCN resectability status	Resectable	Arterial: – No arterial tumor contact	– Well defined, clinically relevant endpoint	– True radiologic downstaging rare	[9]
		Venous: – No tumor contact with the SMV or PV or ≤180° contact without vein irregularity	– Internationally accepted	– No correlation with resection rate and R0 status	
	Borderline[a]	Arterial: – Solid tumor contact with the CHA without extension to the celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction			
		– Solid tumor contact with the SMA ≤180°			
		– Presence of variant arterial anatomy making resection possible			
		Venous: – Solid tumor contact with the SMV or PV >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal the site allowing for safe and complete resection and vein reconstruction			
		– Solid tumor contact with IVC			
	Unresectable[a]	Arterial: – Solid tumor contact with SMA >180°			
		– Solid tumor contact with CA >180°			
		– Solid tumor contact with first jejunal SMA branch			
		Venous: – Unreconstructable SMV/PV due to tumor involvement or occlusion			

Cancer stage	cT0	Primary tumor cannot be assessed	– Good correlation with pathologic T-staging possible	– True radiologic downstaging rare	[49]
	cT1	Tumor limited to the pancreas, 2 cm or less in greatest diameter		– Limited data	
	cT2	Tumor limited to the pancreas, more than 2 cm in greatest diameter			
	cT3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery			
	cT4	Tumor involves the celiac axis or the superior mesenteric artery			
Pattern of recurrence	Local recurrence	–	– Evaluation of local/distant efficacy of preoperative treatment	– Necessitating standardized radiologic follow-up	–
	Peritoneal metastases	–			
	Liver metastases	–			
	Other distant metastases	–			
Surgical					
Resection rate		Number of resected patients/all patients	– Important of surgical success	Biased endpoint as definitions of resectable/unresectable frequently not described	–
		Number of resected patients/explored patients	– Important prognostic endpoint, as resected patients have better survival than unresected	Indications for surgery/resection frequently unclear	
				– Does not correlate with radiologic response	
Exploration rate		Number of explored patients/all patients	– indirect parameter of treatment toxicity	same as above	
Pathologic					
Margin status	R0	Microscopic tumor-free margin	– Most frequently described pathologic parameter	– Standardized pathologic handling necessary	[50, 86]
	R1	Microscopic residual tumor	– Prognostic relevance in PDAC (without pretreatment) established	– Different definitions of R0 between classifications	
	R2	Macroscopic residual tumor		– Description of tumor clearance at all margins (in mm) necessary	
				– No correlation with radiologic response	
Complete pathologic response	pCR	No residual tumor left after neoadjuvant treatment	– Frequently described	– Rare event in PDAC	–
				– Not useful as single response parameter	

(continued)

Table 9.1 (continued)

Response criteria	Groups	Definition	Advantages	Disadvantages	References
Evans score	Grade I	Little (<10 %) or no tumor cell destruction	– Standardized measure of tumor response	– Infrequent use	[60]
	Grade IIa	Destruction of 10–50 % of tumor cells			
	Grade IIb	Destruction of 51–90 % of tumor cells			
	Grade III	Few (<10 %) viable-appearing tumor cells			
	Grade IV	No viable tumor cells			
CAP Score	Grade 0	No viable residual tumor (=pathologic complete response, pCR)	– Semi-standardized measure of tumor response	– Infrequent use	[59]
	Grade 1	Marked response (minimal residual cancer with single cells or small groups of cancer cells)			
	Grade 2	Moderate response (residual cancer outgrown by fibrosis)			
	Grade 3	Poor or no response (extensive residual cancer)			
Biochemical					
CA19-9	–	–	– High positive predictive value	– Low negative predictive value	[62, 63]
				– Not applicable in all PDAC patients	
Survival					
Overall survival	OS	In RCT time from randomization until death from any cause, measured in the intent-to-treat population	– Most objective endpoint	– Differences exist in the calculation of OS (initial diagnosis/beginning of preoperative treatment/ from surgery)	[71, 72]
			– Unbiased		
Disease-free survival	DFS	In RCT DFS is defined as the time from randomization until recurrence of tumor or death from any cause	– Surrogate for clinical benefit given the high morbidity of recurrence	– Less objective than OS	[71, 72]
				– Dependent on radiologic assessment	

Treatment-related					
Toxicity (CTCAE)	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	– Clinically important endpoint to assess toxicity of preoperative treatment	– Impractical for surgical adverse event assessment	[74]
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living	– Well defined for individual toxicities		
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living	– Widely used		
	Grade 4	Life-threatening consequences; urgent intervention indicated			
	Grade 5	Death related to adverse event			
Dindo-Clavien perioperative morbidity	Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions	– Widely used in surgery	– Time-consuming in surgeries with high morbidity	[79]
	Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included	– Objective well-defined endpoints		
	Grade III	Requiring surgical, endoscopic, or radiological intervention			
	Grade IIIa	Intervention not under general anesthesia			
	Grade IIIb	Intervention under general anesthesia			
	Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management			
	Grade IVa	Single organ dysfunction (including dialysis)			
	Grade IVb	Multiorgan dysfunction			
	Grade V	Death of a patient			

BRPC borderline resectable pancreatic cancer, *CA* celiac axis, *CAP* College of the American Pathologists, *CHA* common hepatic artery, *CTCAE* Common Terminology Criteria for Adverse Events, *LAPC* locally advanced, unresectable pancreatic cancer, *NCCN* National Comprehensive Cancer Network, *PV* portal vein, *SMV* superior mesenteric vein

[a]Definition listed only for tumors of the pancreatic head/uncinate process

Radiologic Endpoints

While standardized definitions of BRPC and LAPC were lacking, in recent years the CT-based anatomic classification of BRPC developed at the M.D. Anderson Cancer Center has gained wide acceptance in the USA as it was adopted by the American Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), the Society for Surgery of the Alimentary Tract (SSAT), and the National Comprehensive Cancer Network (NCCN) since 2013 [9] (see section "Radiologic Endpoints"). This definition has recently been adopted by the International Study Group of Pancreatic Surgery (ISGPS) [10]. Prerequisite for this anatomic classification is a multi-detector, thin (submillimeter) CT scan with CT angiography using a pancreatic protocol, with images obtained in the portal venous, arterial, and pancreatic phase of contrast enhancement [9].

Given the CT-based primary staging of BRPC and LAPC, radiologic response evaluation following neoadjuvant treatment seems consequential. Although interobserver variability seems low in CT-based staging of pancreatic cancer [11], current data on this outcome metric is limited.

RECIST

Although Response Evaluation Criteria in Solid Tumors (RECIST) criteria [12] have been well established in other solid tumors, as well as, in metastatic PDAC, its usefulness in response assessment in BRPC/LAPC seems questionable (Table 9.1). In a meta-analysis of 111 trials including more 4394 patient undergoing neoadjuvant treatment for PDAC, only 6 studies explicitly used RECIST criteria for response evaluation and less than 40 % of trials clearly stated their criteria to assess tumor response [13]. Similarly, in trials specifically evaluating neoadjuvant therapy in BRPC, RECIST criteria are used in less than 50 % of cases [14]. In the above-mentioned meta-analysis, the CR rate of all trials (i.e., including those with unclear definitions) was just 3.8 % (95 %CI: 3–4.9 %) and the PR rate 29 % (95 %CI: 26–34 %). Katz et al. could show that in 122 well-characterized BRPC patients at a single-institution, complete remission (CR) following neoadjuvant therapy as defined by RECIST did not occur at all, and that partial response (PR) was rare, occurring in only 15 patients (12 %) [15]. Similar results have been reported by other groups [16, 17].

Resectability Status

Some studies have used the NCCN definitions of resectable, BRPC, LAPC, or metastatic disease to describe response to preoperative therapy. Similar to RECIST data, true radiologic downstaging seems to be a rare event and occurred in just 1 % of the aforementioned study by Katz et al. [15]. In contrast, disease progression and upstaging occurs in roughly 20 % of patients independent of the primary tumor classification [13, 15, 16]. Preliminary data indicate that tumor downstaging might be increased using novel regimes, including FOLFIRINOX and nab-Paclitaxel, which have shown high response rates in the metastatic setting [18–20]. However, radiologic imaging still does not correlate with surgical resection or pathologic response parameters [20] (Fig. 9.1).

Cancer Stage

Other unbiased measures of radiologic response evaluation like radiographic tumor stage following treatment (T-stage) (Table 9.1) or primary tumor diameter before and after preoperative therapy have rarely been reported [14]. Similar to the results of RECIST criteria, the objective response rates for these outcome metrics have been low in BRPC/LAPC [13, 16].

Positron Emission Tomography Imaging

Very limited data exists on positron emission tomography (PET) imaging for response assessment and it has not been tested in large prospective trials so far [21].

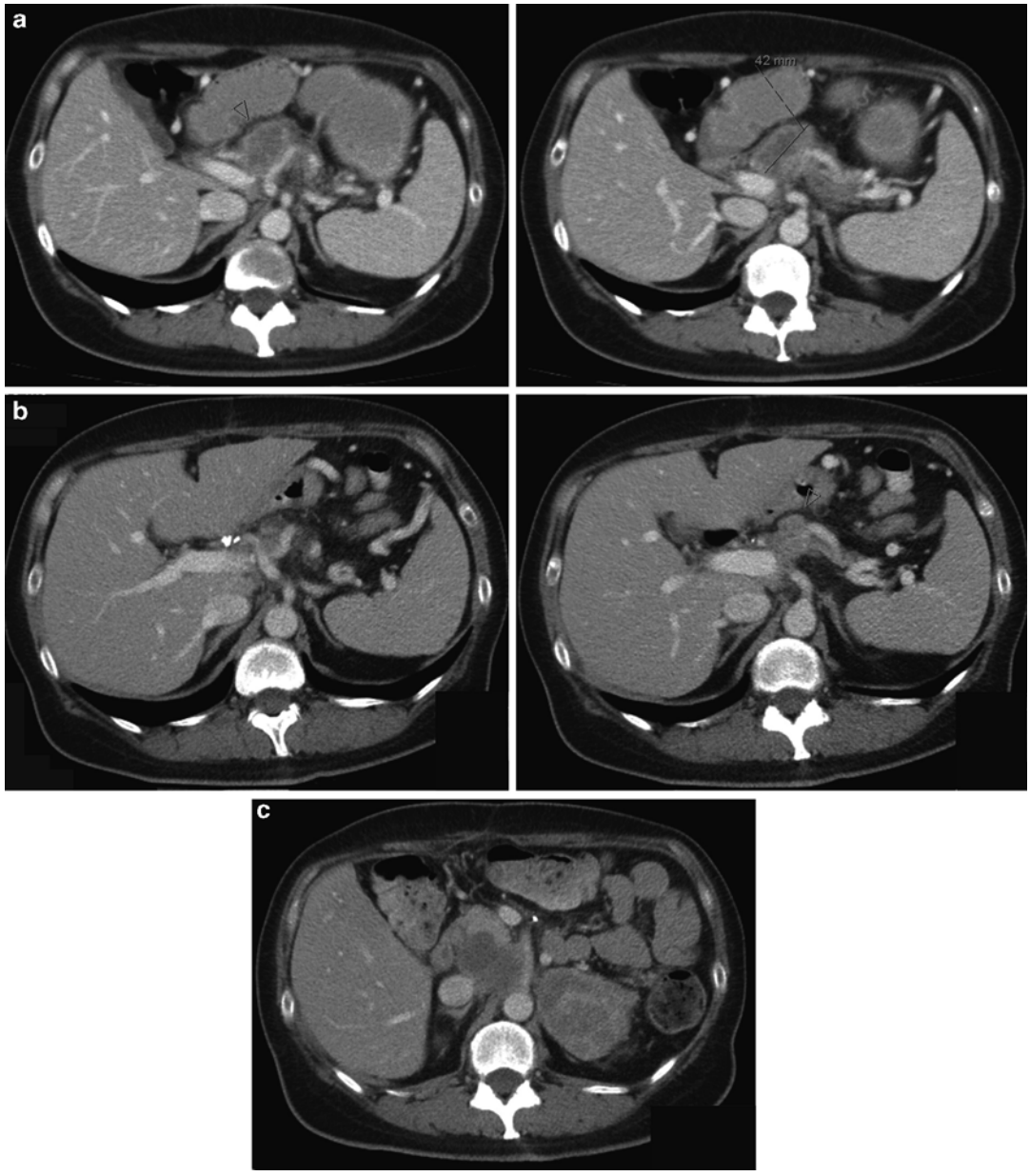

Fig. 9.1 A 53-year-old women with locally advanced adenocarcinoma of the pancreatic body. (**a**) Radiologic staging at primary diagnosis. The tumor was deemed unresectable following laparotomy and exploration due to infiltration of the celiac axis. (**b**) Restaging after 6 cycles of FOLFIRINOX. Radiologic response with tumor regression, but persistent signs of celiac axis infiltration. The patient underwent successful re-exploration and tumor resection with extended distal pancreatectomy, splenectomy, and partial resection of the common hepatic artery with end-to-end anastomosis of the common and proper hepatic arteries. Pathologic analysis revealed a margin-free tumor specimen with minimal clearance of <0.1 cm at the ventral resection margin: UICC-classification (7th edition, 2010): ypT3, ypN0 (0/29), L0, V0, Pn1, G3-4, R0, CRM+ (cranio-dorsal, <0.1 cm ventral), response grade 1 according to Evans. (**c**) Local recurrence 6 months after resection

Pattern of Recurrence

As one of the main arguments in favor of preoperative therapy is the "sterilization" of the tumor bead and occult micrometastases the pattern of recurrence might be used as an important response criterion, but has as yet not been widely used [22]. The ability of PDAC to spread along nerve routes and ganglia causing high rates of local recurrence [23] might be reduced using preoperative regimes. Therefore, tight and standardized radiologic follow-up is recommended in clinical trials of preoperative therapies (Fig. 9.1).

Importantly, all radiologic response measures do not adequately predict surgical exploration and more important resection rates (see below) [13, 16, 24, 25] (Fig. 9.1). While diagnostic sensitivity for arterial involvement as one of the main features of LAPC has been described as high as 97 %, sensitivity has been poor with rates between 67 and 91 % [26–29]. The reason for the inadequate radiological staging of neoadjuvant-treated PDAC seems to be the extensive peritumoral desmoplastic and inflammatory reaction elicited by pancreatic tumor growth and the surrounding stroma [30]. Consequently, microscopic complete pathologic resections (R0) are more frequent than would have been expected by imaging and intraoperative findings (see below).

Until results from ongoing trials with high methodological quality, clear BRPC and LAPC definitions, and sound response classifications based on objective criteria are available [31], the clinical relevance of radiologic response evaluation is limited. Based on current data, radiologic imaging cannot be used to predict successful (R0) surgical resection and its clinical use is therefore limited [15, 17].

Surgical Endpoints

Resection Rate

Resection rates have widely been reported in studies investigating preoperative treatment of BRPC and LACP. In a recent meta-analysis, resection rate was 50.7 % (95 %CI: 44.0–57.4 %) in all patients (i.e., resectable and unresectable at primary diagnoses) undergoing neoadjuvant therapy. As expected resection rates were higher in patients deemed initially resectable (73.6 %; 95 %CI: 65.9–80.6 %) than in patients deemed unresectable at primary diagnosis (33.2 %; 95 %CI: 25.8–41.1 %). Similar rates have been reported in other meta-analysis focusing on BRPC patients [16], radiotherapy [32, 33], phase II trials [34], or specific chemotherapy regimes [35].

These results are frequently interpreted as arguments in favor of neoadjuvant therapy, but have to be interpreted with caution. Surgical resection rate is a highly biased endpoint for preoperative response assessment as: (a) most studies lack clear definitions of resectable, unresectable, BRCP, and LAPC, i.e., inclusion criteria are unclear; (b) the current absence of adequate radiologic staging tools to differentiate between neoplastic and non-neoplastic desmoplasia leads to non-validated treatment decisions; (c) clear indications for surgical exploration and resection are lacking. Therefore, the question of whether these results truly reflect downstaging due to neoadjuvant treatment or whether similar resection rates could have been achieved with direct surgery remains unclear. Results from a multicenter database study indicate that for BRPC with venous involvement only, neoadjuvant therapy does not increase resection rate [36] and is consequently discouraged in some guidelines [10]. Furthermore, as pointed out above, resection rates are generally higher than would have been expected from radiological response assessment. Hence, indication for surgical exploration should be handled liberally until better and more reliable imaging criteria are available.

Surgical Exploration Rate

Surgical exploration rate is a commonly reported endpoint in trials investigating preoperative therapy in PDAC. However, studies limited to BRPC or LAPC are rare. Since preoperative therapy is associated with toxicity and complications and as disease progression may occur during neoadjuvant treatment, the number of patients deemed fit

enough to eventually undergo surgery is an important parameter for the risk and benefit assessment of a preoperative treatment regime. The surgical exploration rate is calculated among all patients in a study in contrast to resection rate, which is often calculated only among those patients that underwent exploration. In their meta-analysis, Gillen et al. reported a surgical exploration rate of 69.5 % (95 %CI: 62.1–76.4 %) in all patients. Exploration rates were higher in patients deemed initially resectable (88.1 %; 95 %CI: 82.9–92.4 %) than in patients deemed unresectable at primary diagnosis (46.9 %; 95 %CI: 36.89–57.1 %). Again, these results have been confirmed by other meta-analyses [16, 32, 34, 35].

However, similar to surgical resection rate, exploration rate is a highly biased parameter. Most trials lack clear definitions of BRPC and LAPC and most studies include heterogeneous cohorts including resectable PDAC patients as well. Furthermore, as clear indications for surgical exploration are not reported, subjective, unblinded, and non-standardized studies may reflect the results of selection bias rather than true benefits of preoperative treatment.

Pathologic Endpoints

Margin Status

Complete microscopic tumor resection (R0) is an important pathologic endpoint in BRPC and LAPC patients, particularly as extended resections including vascular resections are frequently needed. Despite these challenges, the proportion of R0 specimens of all resected patients that underwent neoadjuvant therapy has been reported to be as high as 80 % and seems to differ little between resectable or more advanced cases [13, 16]. In a well-defined, single institution cohort of 85 BRPC patients undergoing neoadjuvant treatment and subsequent resection, the R0 rate was 95 %.

However, comparison between R0 rates in different trials can be hampered by variability in pathologic handling and reporting [37, 38]. Accordingly, the rate of R0 resections dropped from 86 to 24 % in PDAC patients after implementation of a standardized pathological examination protocol [38, 39]. As a consequence, the overall survival benefits of R0 vs. R1 resections in PDAC remains unclear: although a number of studies have demonstrated a significant improvement in median as well as 5-year survival following R0-resection as compared to R1-resection [40–43], others have failed to confirm this association [44–48].

As protocols for pathologic specimen handling have become more standardized in high-volume centers over the last years, difference may still occur due to diverse definitions [10]. While in the USA, the Union for International Cancer Control/AJCC criteria are used, defining R1 when tumor cells are at the resection margin (clearance 0 mm) [49], European guidelines [10] recommend the use of the British Royal College of Pathologists Protocol and the Leeds Pathology Protocol, with tumor clearance of >1 mm demanded for R0 status [50]. However, most guidelines now advise that the tumor clearance (in mm) of all margins should be reported, making comparability possible [9, 10]. This seems particularly import as microscopic margin positivity seems to have different prognostic impact depending on which resection margin is affected [51]. Furthermore, it would allow elucidating the prognostic impact of vascular margin status, frequently observed in BRPC and LAPC resections.

Pathologic Response

Pathologic response is successfully used in a number of solid tumors like rectal or gastric cancer to assess response to preoperative therapy. In PDAC, complete pathologic response (pCR) is reported in a number of trials. Histopathologic pCR in PDAC following neoadjuvant therapy, however, seems to be a rare event, occurring in well less than 10 % of patients [13, 16, 52], even with the latest radiochemotherapy regimes [20]. The reason for this seems to be inherent histopathological characteristics of PDAC-like desmoplasia, complex intratumoral heterogeneity [53], and tumor

microenvironment [30]. Due to its rare occurrence, it remains unclear how pCR correlates with radiologic response. However, prognosis seems to be significantly better for patients with pCR compared to patients with viable cancer cells in the resected specimen [54–56].

Multiple histopathologic response scores, which are well established for other solid tumors like gastric cancer [57], have been proposed for PDAC [58–61], but their clinical usage has been limited. Furthermore, few studies have evaluated the prognostic significance of these classifications. The Evans grading system [60] and the classification by the College of the American Pathologists (CAP) [59] are the best studied scores. Evaluating the Evans and CAP score Chatterjee et al. could show in 223 patients that pCR or minimal residual disease correlated with better survival compared to moderate or poor pathologic response [52].

Other Pathologic Response Endpoints

Numerous studies have shown a decrease in regional lymph node metastases following preoperative therapy in PDAC [22]. Preliminary data indicate that number of positive nodes following neoadjuvant treatment is an independent prognostic marker for survival in this setting [54]. Similarly, the pathologic tumor stage following neoadjuvant treatment (ypT-stage) has been successfully evaluated as response marker [54].

Biochemical Endpoints

Although a number of biochemical response markers have been evaluated in patients undergoing preoperative therapy for PDAC, only CA19-9 has been studied widely enough to be recommended as biochemical response marker. CA19-9 was proposed as preoperative marker in resectable PDAC patients based on results from a large patient cohort, in which CA19-9 levels correlated with resectability, stage of disease and survival [62]. Investigating CA19-9 as response marker Boone et al. could show in a retrospective evaluation of 78 patients that CA19-9 response to neoadjuvant treatment was associated with R0 resection rate, histopathological response and survival [63]. Several smaller studies support the finding that a decline in CA19-9 correlates with response to preoperative treatment in BRPC [64–67] and resectable PDAC [68, 69]. However, a number of limitations have to be considered. Although CA19-9 response seems to have high positive predictive value of >90 %, its low negative predictive value limits clinical usefulness [70]. Furthermore, individual variance of CA19-9 levels is high and some PDAC patients never elicit elevated levels of CA19-9 [62]. Furthermore, no clear cut-off, sensitivity, or specificity analyses are available thereby limiting the clinical utility of CA19-9 as a response marker.

Survival Endpoints

Overall Survival

Overall survival (OS) is a seemingly unbiased endpoint and is considered the most reliable and preferred cancer endpoint by most regulatory agencies [71, 72].

Estimated median survival following preoperative therapy among all patients with PDAC is 22.4 months (95 %CI: 9–62 months) for resected and 9.5 months (95 %CI: 6–21 months) for non-resected patients [73]. Among patients with BRPC, median survival durations as long as 33 months for resected patients have been reported [15]. 1-year and 2-year survival rates for resected patients following preoperative therapy have been reported to be around 78.9 % (95 %CI: 0–100 %) and 49.2 % (95 %CI: 0–82 %), with little difference between initially resectable and non-resectable tumors [13, 16, 35]. In the setting of preoperative treatment trials, however, OS has to be treated with caution as individual trials calculate OS differently. While some studies use the time point of initial diagnosis, others calculate from the start of neoadjuvant therapy, or from surgery/resection [13]. Therefore, standardization is important in future trials.

Disease-Free Survival

Disease-free survival (DFS) is less objective than overall survival, as the problems of radiologic tumor evaluation in PDAC discussed above have to be considered. DFS is a frequently used endpoint for cancers when survival may be prolonged, as overall survival is impractical in this setting. However, this is not the case in recurrent PDAC given the very limited prognosis of these patients. Therefore, given the high frequency and morbidity of early recurrence in BRPC and LAPC (including intractable pain, bowel obstruction, etc.), a significant improvement of DFS might be considered an appropriate endpoint in preoperative treatment trials. In this setting, DFS serves as a surrogate for clinical benefit. Furthermore, DFS as well as OS have been accepted by regulatory agencies for cancer drug approval [71, 72].

Treatment-Related Endpoints, Toxicity, and Prognostic Scores

Toxicity

Toxicity is an important response endpoint during preoperative therapy as it can severely limit quality of like of affected patients. Most frequently, the well-established Common Terminology Criteria for Adverse Events (CTCAE) published by the National Cancer Institute are used [74]. The advantage of the CTCAE is the standardization of reporting and the grading of toxicities. Commonly grade 3/4 toxicities are regarded as severe and clinically relevant. In preoperative treatment trials grade 3/4 toxicity rates of 29.4 % (95 %CI: 23.1–36.1 %) have been reported, but seem to be higher when radiochemotherapy is involved and with more aggressive combination regimens [13].

Morbidity and Mortality

Similarly, postoperative morbidity and mortality rates should be reported, as these are patient-relevant outcomes. Perioperative morbidity and mortality was estimated at 34.2 % (95 %CI: 28.3–40.4 %) and 5.3 % (95 %CI: 4.1–6.8 %) following preoperative therapy [13], i.e., within the range reported for primary surgery [75]. In more advanced tumors including BRPC and LAPC estimates of morbidity and mortality are likely higher [13, 15]. However, postoperative morbidity reporting is frequently not standardized hampering the comparability of different trial results. Standardization by using internationally accepted outcome measures for pancreatic surgery like postoperative pancreatic fistula [76], hemorrhage [77], or delayed gastric emptying [78] are recommended. Similarly, overall postoperative morbidity can be classified and compared using validated scoring systems like the Dindo-Clavien classification [79].

Prognostic Classifications

Given the significant disease burden in BRPC and LAPC and the high rate of toxicity, and perioperative morbidity and mortality, patient selection for preoperative therapy based on current and predicted health status is of obvious importance. Marginal health status after preoperative therapy that precludes subsequent surgical resection is of limited clinical use. Consequently, one of the earliest classifications of BRPC and LAPC, the MD Anderson Cancer Center classification (MDACC) considered patient characteristics as well as anatomic parameters [80].

Some prognostic scores like the modified Glasgow Prognostic score (mGPS) [81–83], CRP-based scores [84], and scoring systems based on circulating white blood cells (e.g., neutrophil/lymphocyte ratio) [84, 85] have been evaluated in PDAC including BRPC. These scores could be used before and after neoadjuvant therapy to select patients for subsequent surgery.

Quality of Life

Few trials investigating preoperative therapies in PDAC have addressed quality-of-life aspects or other patient reported outcomes as primary study endpoint. This seems surprising given the limited overall prognosis and the extensive adverse event

profile of many preoperative therapy regimes. Currently, indirect measures like morbidity and toxicity can be evaluated as surrogate parameter to estimate quality of life in this patient group. Future studies are needed to report and elucidate this aspect.

Conclusion

Response evaluation in BRPC and LAPC following preoperative therapy is complex, and no single parameter currently available is sufficient. Particularly, radiologic parameters do not adequately assess tumor response, most likely due to the complex molecular und histologic features of peritumoral desmoplasia and inflammation. Therefore, a set of radiologic (including multimodal imaging), biochemical, pathologic, and clinical features should be used for response assessment. Standardization and clear definitions for all these aspects are warranted in future studies to improve response evaluation.

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Emerging Systemic and Targeted Therapies

10

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Pancreatic cancer is a systemic disease in the majority of newly diagnosed patients, including those who present with localized resectable disease. Systemic therapy with or without radiotherapy has become a standard of care for patients with localized pancreatic cancer (LPC), (NCCN guidelines version 2.2015), and the role of radiotherapy continues to be debated. Over the past decade there have been an increasing number of systemic agents that have demonstrated clinical benefit in patients with advanced pancreatic cancer. Unfortunately, these advances have been modest at best. Furthermore, despite continued improvements in our knowledge of the molecular biology of pancreas cancer, improvements in survival with multiple target agents have also been poor. The complexity of genetic and epigenetic abnormalities in pancreatic adenocarcinoma and the lack of clear driver mutations challenge the successful development of targeted agents. Newer treatment approaches such as targeting the signal pathways in the stroma and immunotherapy hold promise for the future. In this chapter we will provide an overview of the current therapies, highlight some of the failed treatment strategies, and describe the newer approaches that are currently in development.

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Gemcitabine-Based Regimens

Gemcitabine is established as a component of frontline systemic therapy for localized and metastatic pancreatic cancer. It is a nucleoside analog that inhibits DNA synthesis by blocking ribonucleotide reductase. Gemcitabine is a cell cycle-specific for the S-phase and blocks cellular progression at the G1/S-interphase. In the pivotal phase III study involving 126 patients with locally advanced and metastatic pancreatic cancer, gemcitabine demonstrated a better clinical benefit compared to bolus 5-fluorouracil (5-FU) (23.4 % vs. 4.8 %, $p = 0.0022$). The median survival also improved (5.65 vs. 4.41 months, $p = 0.0025$) in the patients receiving Gemcitabine [1, 2]. Evidence also supports the benefit of gemcitabine in the adjuvant setting following resection of localized pancreatic cancer. In one study, postoperative gemcitabine significantly delayed recurrence of disease after complete resection compared to observation alone. Median disease-free survival was 13.4 months in the gemcitabine group vs. 6.9 months in the control group ($P < 0.001$) [3]. Based on these results, single agent gemcitabine has become the standard systemic therapy for patients with pancreatic cancer irrespective of stage. However, benefit, as a single agent was perceived to be very modest or even marginal.

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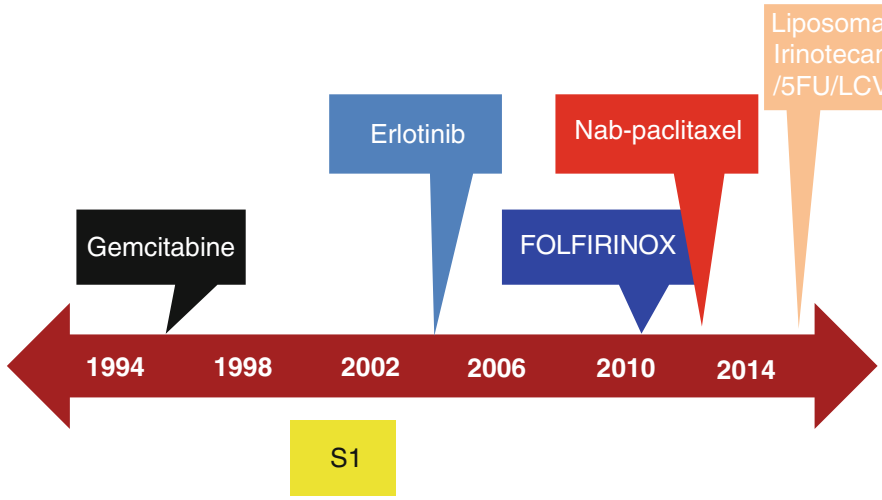

Fig. 10.1 Development of new drugs and regimens in the treatment of pancreatic cancer. Drugs or regimen activity demonstrated in a phase III study. Not all agents are approved by the FDA

Gemcitabine in combination with either a cytotoxic drug or a targeted agent has also been studied in numerous phase II and III clinical trials in patients with advanced pancreatic cancer including those with LAPC. The combination of gemcitabine plus a fluoropyrimidine, a platinum compounds, and Irinotecan or pemetrexed amongst others did not show significant improvement of overall survival when compared to gemcitabine alone despite promising pilot trials [4, 5]. Therefore, at this time such combinations are rarely used in treating patients with advanced pancreatic cancer especially with the advent of the gemcitabine-nab-paclitaxel combination (see below).

S-1

S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-FU combined with two 5-FU biochemical modulators: 5-chloro-2,4-dihydropyridine (gimeracil or CHDP), a competitive inhibitor of dihydropyrimidine dehydrogenase and oteracil potassium which inhibits phosphorylation of 5-FU in the gastrointestinal tract decreasing toxicities such as nausea, vomiting, stomatitis, and diarrhea [6]. A phase III study involving 834 patients with locally advanced or metastatic pancreatic cancer, patients were randomized to receive gemcitabine alone ($n=277$), S-1 alone ($n=280$) or gemcitabine plus S-1 combination ($n=275$). This study was conducted in Japan and Taiwan to assess the *non*-inferiority of S-1 to gemcitabine. The median overall survival was 8.8 months in gemcitabine group, 9.7 months in the S-1 group, and 10.1 months in the gemcitabine plus S-1 group. The trial showed that S-1 was noninferior to gemcitabine with a hazard ratio of 0.96; 97.5 % CI 0.78–1.18, $P<0.001$. The superiority of gemcitabine plus S-1 was not demonstrated (HR 0.88, 97.5 % CI 0.71–1.08, $p<0.15$) [7]. Based on this trial S-1 is currently approved in Japan as monotherapy for the treatment of patients with advanced pancreatic cancer (Fig. 10.1).

FOLFIRINOX

In a phase II/III French study, 342 patients with metastatic pancreatic cancer and good performance status (ECOG 0 or 1) were randomly assigned to FOLFIRINOX (oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2, leucovorin, 400 mg/m^2,

and 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 given as a 46-h continuous infusion, every 2 weeks) or gemcitabine at a standard dose and schedule. The median overall survival was significantly longer in the FOLFIRINOX group of 11.1 months as compared with 6.8 months in the gemcitabine group (HR, 0.57, 95 % CI, 0.45–0.73, $p<0.001$). Similarly median progression-free survival was 6.4 months in FOLFIRINOX arm and 3.3 months in gemcitabine group (HR for disease progression, 0.47, 95 % CI 0.37–0.59; $p<0.001$). Incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were significantly higher in the FOLFIRINOX group [8]. There are no mature randomized trials that have evaluated FOLFIRINOX in locally advanced pancreatic cancer or in resectable localized disease.

Nanoparticle Albumin-Bound Paclitaxel (Nab-Paclitaxel) and Gemcitabine

The combined antitumor activity of nab-paclitaxel with gemcitabine was evaluated in a large phase III clinical trial. Eight hundred and sixty-one patients with metastatic pancreatic cancer were randomized to receive gemcitabine plus nab-paclitaxel or gemcitabine alone. The median overall survival was 8.5 months in the nab-paclitaxel plus gemcitabine arm compared to 6.7 months in the gemcitabine arm (HR for death 0.72; 95 % CI 0.62–0.83, $p<0.001$). The progression-free survival was 5.5 months in the combination group vs. 3.7 months in the single agent gemcitabine group (HR for disease progression or death 0.69, 95 % CI 0.58–0.82, $P<0.001$). As to be expected there were more febrile neutropenia and peripheral neuropathy in the combination group [10]. Based on this clinical trial, nab-paclitaxel plus gemcitabine was approved by the FDA and was established as a standard of care alongside FOLFIRINOX in patients with advanced pancreatic cancer. There is no head-to-head comparison between the two regimens in advanced disease. The Nab-paclitaxel/gemcitabine regimen is currently being investigated in patients with resected pancreatic cancer in a Phase III trial versus single agent gemcitabine.

TH-302 and Gemcitabine

As tumors grow, it rapidly outgrows its blood supply resulting in a hypoxic environment within the tumor. The hypoxic microenvironment in many solid tumors including pancreatic cancer induces alterations in tumor biology, promoting invasion, angiogenesis, drug resistance, and metastases. Conventional cytotoxic agents typically target actively dividing cells near the tumor vasculature. Tumor cells within the hypoxic region of tumors are relatively quiescent making them resistant to conventional chemotherapy and radiotherapy. Traditional cytotoxic drugs have poor penetrance into the hypoxic regions of the tumor, resulting in decrease concentration of these cytotoxic agents within that microenvironment leading to treatment failure. TH-302 (evofosfamide) is a hypoxia-activated cytotoxic prodrug currently being developed for the treatment of advanced pancreatic cancer and other solid tumors. Evofosfamide is a 2-nitroimidazole prodrug designed to release DNA cross-linker bromo-iphosphoramide mustard (Br-IPM) when reduced by intracellular reductase in the setting of severe hypoxia. Once released, Br-IPM also diffuses to adjacent cells in normoxic regions of the tumor. In a phase II study, 214 patients with locally advanced or metastatic pancreatic cancer were randomized to receive gemcitabine alone, gemcitabine plus TH 302 (240 mg/m^2) or gemcitabine plus TH-302 (340 mg/m^2). Median PFS was 5.6 vs. 3.6 months (HR, 0.61; 95 % CI, 0.43–0.87; $P=0.005$). Median OS was 7.6 vs. 6.3 months for metastatic disease and 13.1 vs. 15 months for locally advanced disease with the combinations compared with gemcitabine alone [11]. Based on this trial, a global phase III clinical trial (MAESTRO; NCT01746979) comparing gemcitabine plus TH-302 at 340 mg/m^2 vs. gemcitabine plus placebo was recently completed to evaluate efficacy with the primary end point being overall survival.

Liposomal Irinotecan (MM-398) and 5-FU/Leucovorin

MM-398 (liposomal irinotecan) is a nanoliposomal encapsulated prodrug of irinotecan with approximately 80,000 molecules of irinotecan stably encapsulated in a 100 nm liposome. This liposomal encapsulation extends the plasma half-life of the drug and improves normal tissue/tumor biodistribution resulting in improved antitumor activity with lesser toxicity [12]. Based on a phase II study showing moderate antitumor activity against gemcitabine refractory metastatic pancreatic cancer [13], a large multicenter phase III study NAPOLI-1 was completed. In this three-arm study, patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy were randomized to M-398 (iv 120 mg/m^2 every 3 weeks) ($n=118$), 5-FU and leucovorin alone (iv 2000/200 mg/m^2 weekly×4 every 6 weeks) ($n=119$), and the combination of MM-398 [(iv 80 mg/m^2) plus 5-FU/LV (2400/400 mg/m^2) every 2 weeks] ($n=117$). The overall survival in the MM-398 plus 5-FU/LV was 6.1 months (95 % CI 4.8–8.9) (stratified HR for death 0.57 (95 % CI 0.41–0.80), $p=0.009$). Similarly, median PFS was 3.1 months (95 % CI 2.7–4.2) vs. 1.5 months, (95 % CI 1.4–1.8), $p=0.0001$ in the MM-398 plus 5-FU/LV group vs. 5-FU/LV respectively. There was no significant difference in overall survival between MM-398 alone vs. 5-FU/LV alone group. The most common grade 3 or more adverse effects were fatigue 14 %, diarrhea (13 %), and vomiting (11 %). The most common grade 3 or more hematologic adverse effects was neutropenia (20 %) [14]. Currently, MM-398 is pending FDA approval for second-line therapy after gemcitabine-based therapy failures. There is no data on the comparative effectiveness of MM-398 versus regular irinotecan.

Targeted Agents

Targeting HER and IGF-1R Pathways

Several studies have reported that overexpression of HER2/neu or gene amplification in 11–16 % of metastatic pancreatic ductal adenocarcinoma [15, 16]. Trastuzumab is a humanized IgG kappa monoclonal antibody that selectively binds with extracellular domain of epidermal growth factor receptor protein, HER2, causing inhibition of the proliferation of human tumor cells that overexpresses HER2. Trastuzumab in combination with capecitabine and gemcitabine has been evaluated in phase II clinical trials in patients with advance pancreatic cancer. Addition of trastuzumab with capecitabine or gemcitabine did not significantly improve OS or PFS as compared to single agent capecitabine or gemcitabine [15, 16].

Insulin-like growth factor-1 (IGF-1) activates its receptor IGF-1R leading to activation of the PI3 kinase pathway which leads to cell growth and proliferation, as well as, provide antiapoptotic signals to premalignant and malignant cells [17]. In pancreatic cancer, IGF-1 and its receptor are aberrantly expressed or activated [18–20]. AMG 479 (ganitumab) is a human monoclonal antibody against IGF-1R that has shown additive antitumor activities in combination with gemcitabine against malignant pancreatic cancer cells both in vitro and in vivo [21]. Conatumumab (AMG655) is a human monoclonal antibody against the TRAIL receptor 2 (tumor necrosis factor-related apoptosis-inducing ligand) that induces apoptosis [22]. In a randomized, placebo-controlled phase II study, ganitumab and conatumumab were evaluated in combination with gemcitabine in patients with metastatic pancreatic cancer. Both ganitumab and conatumumab demonstrated trends toward an improved survival at 6 months [23]. Based on this trial result, a phase III placebo control clinical trial (clinical trial: NCT01231347) was conducted utilizing combination AMG 479 (ganitumab) and gemcitabine. Based on preplanned interim analysis, the data monitoring committee decided to stop the trial. The data monitoring committee concluded that the addition of ganitumab to gemcitabine was unlikely to significantly improve overall survival.

Erlotinib, an oral EGFR tyrosine kinase inhibitor was tested in a phase III double-blind, placebo-controlled study in patients with locally advanced or metastatic pancreatic cancer. Erlotinib 100 mg/day was combined with gemcitabine and resulted in a significantly longer

overall survival when compared to gemcitabine alone (HR = 0.82, $p = 0.038$). However, the benefit was deemed clinically less meaningful because of a very marginal improvement in the median survival (6.24 vs. 5.91 months) and 1-year survival rate (23 % vs. 17 %) [24]. Increased toxicity and cost, as well as, the lack of a clinical biomarker that could identify responsive patients have made the use of erlotinib obsolete. Erlotinib in combination with gemcitabine was also tested in patients with pancreatic cancer after complete resection. This phase III study did not show any survival advantage for patients receiving erlotinib plus gemcitabine compared to gemcitabine alone in the adjuvant setting [25]. Similarly, the use of erlotinib was tested in patients with LAPC in the LAP 07 study. The addition of erlotinib to gemcitabine did not show survival advantage [26]. The monoclonal antibody cetuximab has also been investigated in patients with advanced pancreatic cancer in combination with gemcitabine. In a large phase III clinical trial involving 745 patients with locally advanced or metastatic pancreatic adenocarcinoma, efficacy of cetuximab in combination with gemcitabine ($n = 372$) vs. gemcitabine ($n = 372$) alone was investigated. This study found that there was no difference in median survival (6.3 vs. 5.9 months, HR 1.06; 95 % CI 0.91–1.23, $p = 0.23$) between the combination arms vs. gemcitabine alone. Despite, 92 % of the patients having EGFR positive tumors, there were no differences in median survival in either arm (median OS 6 months, HR 0.98; 95 % CI 0.83–1.17; $p = 0.42$) [27]. Overall, targeting EGFR in patients with localized or advanced pancreatic cancer without patient selection is not a valid therapeutic strategy.

Targeting Vascular Endothelial Growth Factor/Receptor Pathway

The Vascular endothelial growth factor/receptor (VEGF/VEGFR) pathway was actively investigated in patients with advanced pancreatic cancer. This included testing of anti-VEGF and anti-VEGFR treatment strategies with drugs added to a backbone of chemotherapy consisting of gemcitabine. Addition of bevacizumab in combination with erlotinib and gemcitabine or gemcitabine in patients with metastatic pancreatic cancer has failed to demonstrate a survival benefit [28]. Axitinib is a tyrosine kinase inhibitor of VEGF receptors used in treatment of metastatic renal cell carcinoma. The addition of axitinib to gemcitabine has not improved overall survival in advanced pancreatic cancer [23]. Sorafenib is a multi-targeted kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor (PDGF) receptor and RAF kinase. It is currently approved for the treatment for advanced renal cell carcinoma and hepatocellular carcinoma. In a placebo-controlled, double-blind phase III study, the efficacy of gemcitabine plus sorafenib ($n = 52$) compared to gemcitabine and placebo ($n = 52$) was evaluated in patients with advanced pancreatic cancer. The addition of sorafenib to gemcitabine did not improve response rate or overall survival [29]. This negative result was consistent with a phase II study conducted by El-Khoueiry comparing combination of gemcitabine plus sorafenib with sorafenib alone [30]. Aflibercept is a VEGF inhibitor that binds with circulating VEGFs causing failure of initiation of VEGF-ligand-dependent signaling pathway. In a preclinical and phase I study, aflibercept demonstrated antitumor activity and was well tolerated [31, 32]. The efficacy of aflibercept was tested in patients with metastatic pancreatic cancer in combination with gemcitabine. In a large phase III double-blind clinical trail, 546 patients with metastatic pancreatic cancer were randomized to aflibercept plus gemcitabine group ($n = 271$) or gemcitabine plus placebo ($n = 275$). Preplanned interim analysis conducted on 427 patients failed to show a survival benefit for the aflibercept group and the study was terminated early [33].

At this time, targeting the VEGF/VEGFR pathway is considered to be a failed therapeutic strategy, partly explained by the poorly vascularized nature of pancreatic cancer.

Targeting NOTCH and JAK/STAT Pathway

Global genomic analysis of pancreatic cancer has revealed that pancreatic cancers contain an average of 63 genetic alterations, majority of them are point mutations in a core set of 12 cellular signaling pathways. The WNT/Notch pathway is dysregulated in 100 % of pancreatic cancers [34]. The Notch signaling pathway plays an important role in the embryonic development of the pancreas [35] and the Notch targeted genes are upregulated in invasive pancreatic cancers, and are involved in the progression of pancreatic cancer from pancreatic intraepithelial neoplasia (PIEN) [36–38]. MRK-003 is a potent gamma-secretase inhibitor, which downregulates the nuclear Notch 1 intracellular domain resulting in the inhibition of cellular growth. Preclinical studies in mice demonstrated that MRK-003 in combination with gemcitabine prolongs survival [39]. Janus kinase (JAK) and the activation of downstream signal transducer and activator of transcription 3 (STAT3) play important roles in the progression of pancreatic cancer [40, 41]. Inhibition of STAT3 activities with Janus Kinase-specific inhibitor AG490 suppresses the growth of pancreatic cancer cells [42]. A recent preclinical study has shown that targeting Notch and JAK2/STAT3 signaling pathways with gamma-secretase inhibitor IX and AG-490 concurrently is superior in inhibiting pancreatic cancer progression, then a single inhibitor alone [43].

Ruxolitinib is a selective inhibitor of Janus Kinase (JAK1 and JAK2) tyrosine kinase. It is currently approved for the treatment of myelofibrosis with mutation of JAK2V617F and provides significant improvement in cytokines-mediated symptoms [44]. Given patients with advance pancreatic cancer have evidence of systemic inflammations as evident by cachexia, muscle loss, and poor performance status, a phase II study was conducted in patients with metastatic pancreatic cancer that were refractory to chemotherapy. Patients were randomized to ruxolitinib plus capecitabine ($n=64$) or capecitabine plus placebo ($n=63$). Multivariate analysis of overall survival in subgroups of patients with CRP (c-reactive protein) more than 13 g/mL showed survival advantage in the ruxolitinib combination group as compared to placebo group with HR for death of 0.47 (95 % CI 0.26–0.85); $p=0.01$ [45]. Based on this trial, a randomized, double-blind phase III study is underway evaluating ruxolitinib or placebo in combination with capecitabine in patients with advanced pancreatic cancer with serum CRP levels of ≥10 g/mL (NCT02119663).

Targeting DNA Repair-Deficient Cells

Recent work has identified DNA repair-deficient pancreatic cancers such as those with *BRCA* mutations to be susceptible to cell kill by platinum compounds and also by PARP inhibitors. Ongoing clinical trials are investigating these treatment strategies in patients with advanced pancreatic cancers.

Degrading Hyaluronan

Hyaluronan is the component of the stroma that is considered to establish a barrier to the effective delivery of cytotoxic drugs to tumor cells in addition to other biological functions promoting carcinogenesis and tumor progression. Preclinical studies have demonstrated that targeting the hyaluronan with hyaluronidase would increase the killing of tumor cells and improve survival of mice treated with gemcitabine. Pegylated hyaluronidase is currently being tested in two major randomized clinical trials in patients with metastatic pancreatic cancer in combination with either gemcitabine/nab-paclitaxel (supported by Halozyme) or FOLFIRINOX (supported by the Southwest Oncology Group). Interim data from the ongoing study with gemcitabine and nab-paclitaxel suggested a benefit of the pegylated hyaluronidase in patients who have high tumoral expression levels of hyaluronan measured by immunohistochemistry.

Immunotherapy

The benefits of immunotherapy have long been appreciated in hematologic malignancies and the graft versus leukemia effect of donor transfusion lymphocytes is a well-established knowledge [46]. Recent advances of immunotherapy in solid tumors are showing promising results such as Sipuleucel-T for prostate cancer [47], and ipilimumab for melanoma [48]. The recent evolution of cancer vaccines has been encouraging. GVAX is an irradiated allogeneic granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting pancreatic tumor vaccine [49]. It is administered 24 h after treatment with low-dose cyclophosphamide with intention to regulate CD8+ T cells. GVAX activates CD8+ T cells against various antigens of pancreatic cancer and mesothelin [50]. Activation of mesothelin-specific CD8-T cells has been correlated with improved disease-free survival [51]. CRS-207 is a recombinant live-attenuated, Listeria monocytogenes that has been engineered to express human cancer antigen mesothelin that get processed and get presented to major histocompatibility complex class I and class II [52]. GVAX and CRS-207 have been evaluated in pancreatic cancer in a phase II study in patients with metastatic pancreatic cancer. The use of cyclophosphamide followed by GVAX as priming vaccines and CRS-207 as a booster resulted in improved overall survival with minimum toxicity [53]. Based on this promising result, a phase 2b ECLIPSE trial has been designed for patient with metastatic pancreatic cancer with the intention to recruit 300 patients [54]. At this time the activity of immune checkpoint inhibitors have not been established in pancreatic cancer.

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Part 4

Surgery

Operative Principles in Managing Patients with Borderline Resectable Pancreas Cancer

11

Kaitlyn J. Kelly and Andrew M. Lowy

Abbreviations

BRPC	Borderline resectable pancreas cancer
CA 19-9	Carbohydrate antigen 19-9
CR-PF	Clinically relevant pancreatic fistula
DGE	Delayed gastric emptying
DP	Distal pancreatectomy
GDA	Gastroduodenal artery
JP	Jackson-Pratt
PD	Pancreaticoduodenectomy
PF	Pancreatic fistula
PG	Pancreaticogastrostomy
PJ	Pancreaticojejunostomy
PPH	Post-pancreatectomy hemorrhage
PPPD	Pylorus-preserving pancreaticoduodenectomy
RAMPS	Radical antegrade modular pancreatosplenectomy
SL	Staging laparoscopy
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
TP	Total pancreatectomy

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Introduction

Borderline resectable pancreatic cancer (BRPC) is a complex disease entity and should be managed at a high-volume, tertiary care center with a multidisciplinary team of specialists. Involvement of an experienced pancreatic surgeon early in the course of a patient's treatment is crucial so that surgical resection, arguably the most important component of therapy, can be delivered safely, effectively, and at the optimal time in the sequence of treatment.

Timing of Surgery

The goal of surgery for BRPC is margin-negative (R0) resection and ultimately long-term survival. Patients who undergo upfront resection with macroscopically positive margins have outcomes similar to patients who receive definitive chemoradiation without surgery, but with significant morbidity. Even in the instance of microscopically positive margins, survival is markedly reduced. Therefore, margin-positive resection should be avoided at all costs. Additionally, even after R0 resection, many patients go on to develop distant metastatic disease in the very early postoperative period. While there is currently no test available to definitively identify these patients, several indicators of aggressive disease biology are well recognized. Such considerations have

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led to the predominant use of neoadjuvant or preoperative therapy for patients with BRPC. Despite this, the best means to define the timing of surgery remain elusive.

Multiple factors must be considered in deciding the optimal timing of surgery for patients with BRPC. These include patient's age, performance and nutritional status, anatomic considerations for borderline resectability (venous or arterial involvement), clinical node status, and serum carbohydrate antigen 19-9 (CA 19-9) level. Patients often prefer a surgery-first approach, as they feel that immediate extirpation of the tumor is the best treatment. It takes time and communication skills to explain why a margin-positive resection or a resection in the setting of aggressive disease biology is not indicated.

Patient Factors

Patients with advanced age, poor performance status, and/or significant comorbidities who are particularly at high-risk for surgery may be best treated with neoadjuvant therapy regardless of whether they have radiographically resectable or borderline resectable disease. These patients are often not candidates for aggressive neoadjuvant therapy regimens, such as FOLFIRINOX, for the same reasons they are not good candidates for surgery. Gemcitabine-based regimens (i.e., gemcitabine plus nab-paclitaxel or gemcitabine with radiation) are often utilized. If patients tolerate therapy well and do not develop distant metastasis during neoadjuvant treatment, they have withstood a "test of time," so to speak. Surgical resection may then be recommended with somewhat more assurance that the patient may tolerate and recover from the demands of surgery. Furthermore, if these high-risk patients do develop complications from surgery that preclude adjuvant therapy, they will have already received systemic treatment (Fig. 11.1).

Anatomic Factors

Neoadjuvant therapy should be offered to all patients with anatomic BRPC as defined in "Introduction." These patients are highly likely to require major vascular resection and reconstruction and by definition are at increased risk for a margin-positive resection. This is particularly true for patients with arterial involvement. In such cases, even focal or localized involvement can be associated with microscopic extension of cancer cells along the periarterial lymphatic and neural plexuses that ultimately

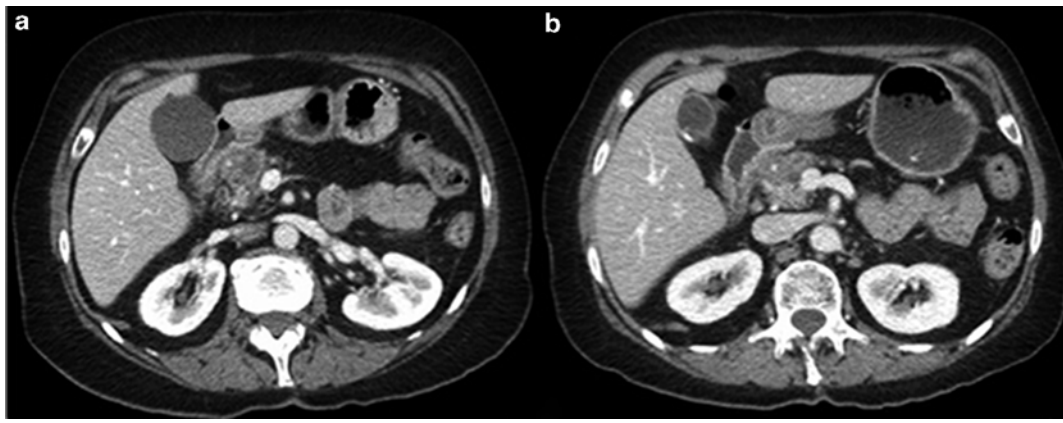

Fig. 11.1 Computed tomography scan of patient with BRPC due to hepatic arterial involvement both before (**a**) and after (**b**) neoadjuvant therapy with FOLFIRINOX. The tumor can be seen encasing the gastroduodenal artery (GDA) in both images. It extended up the GDA and directly contacted the hepatic artery, and this did not change following neoadjuvant treatment

result in a microscopically positive resection margin. This is not typically true for patients with BRPC due to isolated vein involvement. While we prefer neoadjuvant therapy for all patients with BRPC, a surgery-first approach may be a reasonable option for fit patients with isolated vein involvement, especially those who are jaundiced and would require endoscopic or percutaneous biliary drainage in order to receive neoadjuvant treatment, and those in whom a tissue diagnosis cannot be obtained.

Disease Biology

In addition to patient and tumor-related factors, disease biology must be considered in decisions regarding timing of surgery. Patients with clinical evidence of regional lymph node metastasis and those with markedly elevated serum CA 19-9 levels at presentation are more likely to harbor radiographically occult distant metastasis. These patients are at risk of developing early systemic recurrence following surgery and should be treated with systemic therapy first.

Summary

Once patient, tumor, and disease biology-related factors have been assessed, an experienced surgeon can make a recommendation regarding the optimal timing of surgery for a patient with BRPC. This recommendation should be discussed in a multidisciplinary setting. In cases where neoadjuvant therapy is recommended, available regimens, including clinical trials, should be discussed and the timing of re-staging and surgical follow-up should be established.

Operative Principles

Whether patients receive neoadjuvant therapy or upfront surgical resection, the principles of surgery for BRPC are the same. The goal of surgery is complete, R0 resection with minimal morbidity. Neoadjuvant therapy is thought to improve the likelihood of R0 resection for BRPC, but it rarely changes the extent of resection necessary [1]. As illustrated in Fig. 11.2, if patients have evidence of vascular involvement at presentation, the need for vascular resection and reconstruction is unlikely to change the following neoadjuvant treatment. This chapter discusses basic operative principles of pancreatic resection and summarizes current data regarding variations in surgical technique and perioperative care that have been proposed to minimize morbidity. Techniques of vascular resection and reconstruction will be discussed in subsequent chapters.

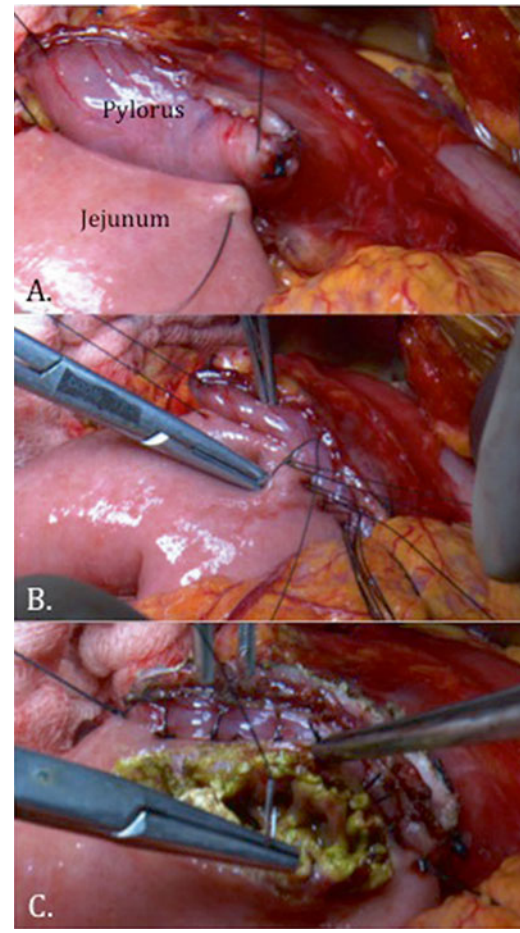

Fig. 11.2 Intraoperative photograph of reconstruction during pylorus-preserving pancreaticoduodenectomy. (**a**) The duodenum is divided just distal to the pylorus and is approximated to the jejunal limb in an end-to-side fashion. (**b**, **c**) A hand-sewn, double-layered duodenojejunostomy is performed

Staging Laparoscopy

Laparoscopy has been investigated as a staging tool in pancreatic cancer given the high incidence of synchronous metastasis and the poor sensitivity of cross-sectional imaging for detection of small-volume peritoneal surface lesions. Staging laparoscopy (SL) consists of gross inspection of the peritoneal cavity with biopsy of any abnormal or suspicious appearing lesions and can be performed under the same anesthetic as surgical resection, or can be performed as a separate procedure prior to planned resection. If performed separately, peritoneal washings can be obtained for cytologic analysis. Positive peritoneal cytology is considered M1 disease.

Multiple studies have been conducted evaluating the yield of SL for the detection of radiographically occult metastatic disease in patients with pancreatic cancer. The overall yield of detection of radiographically occult metastasis ranges from 14 to 30 % [2–5]. Most of these studies consisted of heterogeneous patient populations, however, including patients with both resectable and borderline resectable disease, and some included patients with histological diagnoses other than pancreatic cancer. Improvements in imaging are ongoing and thus the true yield of SL and cost-effectiveness is difficult to determine accurately [5]. As a result, the routine use of SL for patients with pancreatic cancer has not been widely adopted.

The yield of SL in patients with BRPC is likely higher. Most practitioners agree that there is a role for the selective use of SL in patients with pancreatic cancer at high-risk for occult metastasis and who do not otherwise require a laparotomy for any type of palliative procedure. This includes patients with BRPC, body/tail tumors which tend to present at a later stage, tumors >3 cm in diameter, elevated CA 19-9 (>4 times upper limit of normal), enlarged regional lymph nodes, and findings concerning but equivocal for metastases on cross-sectional imaging [6, 7]. Additionally, SL with peritoneal washings should be strongly considered for patients with BRPC for whom neoadjuvant therapy is planned, particularly if on a clinical trial. SL may also be useful to rule out radiographically occult systemic disease prior to the administration of radiotherapy, if that modality is being used.

Pancreatic Resection

Surgical options for pancreatic adenocarcinoma include distal pancreatectomy with splenectomy (DP), pancreaticoduodenectomy (PD), and in rare cases, total pancreatectomy (TP). Lesser resections such as enucleation, central pancreatectomy, and spleen-preserving distal pancreatectomy do not achieve a sufficient regional lymphadenectomy and are not recommended for pancreatic adenocarcinoma.

Distal Pancreatectomy with Splenectomy

DP with en bloc splenectomy is indicated for tumors of the body and tail of the pancreas. These tumors are generally more advanced at presentation than tumors arising in the head of the gland, because they do not result in jaundice and therefore usually present with pain and/or weight loss when they are large. The first step in DP is entering the lesser sac by opening the gastrocolic ligament. This dissection is extended up along the greater curvature of the stomach through the short gastric vessels, to the left crus of the diaphragm. There are usually filmy attachments between the posterior wall of the stomach and the capsule of the pancreas that need to be divided.

Once the body and tail of the pancreas are exposed, the lesion is identified. This may be obvious in cases of large masses, but may require intraoperative ultrasound for small, incidentally identified lesions. A pancreatic transection site proximal to the lesion, ideally several centimeters away, is then selected. The inferior border of the pancreas, which is generally an avascular plane, is then mobilized. The splenic artery is identified at its origin from the celiac axis and should be encircled with a vessel loop. The splenic artery and vein may be divided en bloc with the pancreas for very distal tumors, but often

need to be divided at their origins, outside of the pancreas for more proximally located tumors. In this case, the artery should be divided first. For large, bulky tumors, it may be helpful to mobilize the lateral attachments of the spleen as the first step so that the spleen and distal pancreas can be rotated up and extracorporealized to facilitate the posterior dissection. For tumors invading the stomach, left adrenal gland, or transverse mesocolon, en bloc resections of these organs should be performed to achieve clear margins. The inferior mesenteric vein may or may not need to be ligated and divided, depending on its insertion site along the superior mesenteric vein (SMV)/splenic vein.

The technique of radical antegrade modular pancreatosplenectomy (RAMPS) was first proposed in 2003 as a means of ensuring microscopically negative tangential margins and adequate lymphadenectomy [8]. RAMPS is a modification of standard DP/splenectomy that entails early division of the neck of the pancreas and splenic vessels, lymphadenectomy including periportal, hepatic artery, and celiac axis nodes, and posterior plane of dissection along the anterior surface of the adrenal gland and including Gerota's fascia. Given the lack of controlled data and the predominant systemic recurrence pattern of pancreatic cancer, the relative value of this approach remains unclear.

A topic of debate regarding DP is focused on the best method of transection of the pancreas to minimize the rate of leaking of pancreatic exocrine fluid from the divided stump. Leaks lead to intra-abdominal fluid collections, abscesses, and once drained, pancreatic fistula (PF). Multiple techniques have been investigated, including sharp or cautery transection with oversewing of the stump, use of fibrin glue, and soft tissue reinforcement with omental or falciform patches, and stapled transection with or without bioabsorbable mesh reinforcement. None of these methods have been definitively shown to be superior to others.

Staple line reinforcement with bioabsorbable mesh has been investigated in multiple retrospective studies with conflicting results [9–11]. These studies prompted a randomized, prospective trial comparing stapled transection of the pancreas with or without bioabsorbable mesh, which demonstrated a significant decrease in clinically relevant PF (CR-PF) with use of mesh reinforcement (2 % vs. 20 %, $p<0.001$) [12]. Despite these findings, this technique has not been widely accepted. Information on pancreatic duct diameter and parenchymal consistency in the two groups was not reported, and many question the validity of the results given the extremely low rate of PF in the mesh group. Decisions regarding the optimal method of transection should be made at the time of surgery. We prefer stapled transection with bioabsorbable reinforcement for soft, normal-textured glands, and oversewing for thick, firm glands that cannot be compressed with a stapler.

Pancreaticoduodenectomy

PD is the most commonly performed operation for pancreatic adenocarcinoma, as 60–70 % of tumors arise in the head of the pancreas, and is the primary focus of this chapter. PD is a technically challenging and complex procedure. Since it was first performed as a two-stage operation by Dr. Allen O. Whipple in 1935, significant advances have been made in surgical technique and perioperative care. Operative mortality is now generally <3 % at high-volume centers, but postoperative morbidity remains high, on the order of 30–50 % [13, 14]. In addition to general infectious and cardiopulmonary complications that can occur after any major surgery, well-defined complications associated particularly with PD include delayed gastric emptying (DGE), PF, and post-pancreatectomy hemorrhage (PPH) [15–17]. These definitions are summarized in Table 11.1.

Standard PD involves removal of the head of the pancreas, antrum of the stomach, duodenum, gallbladder, common bile duct, and regional lymph nodes. Regional nodes include those of the porta hepatis to the right of the hepatoduodenal ligament, those in the retroperitoneum to the right of the superior mesenteric artery (SMA), and the anterior and posterior pancreaticoduodenal nodes. The hepatic artery lymph node is also

Table 11.1 International Study Group of Pancreatic Surgery definitions of characteristic post-pancreatectomy complications

Complication	Definition	Grade A	Grade B	Grade C
DGE [15]	Inability to return to a standard diet by the end of the first postoperative week, in the absence of mechanical obstruction	NGT still required 4–7 days after surgery, or NGT reinserted on or after postoperative day #3	NGT still required 8–14 days after surgery, or NGT reinserted on or after postoperative day #7	NGT still required >14 days after surgery, or NGT reinserted on or after postoperative day #14
PF [14]	Drain output of any measurable volume on or after postoperative day #3 with amylase content >3 times the serum amylase			
	Clinical condition	Well	Often well	Appearing ill
	Specific treatment required	No	Yes/no	Yes
	US/CT (if obtained)	Negative	Negative/positive	Positive
	Persistent drainage (>3 weeks)	No	Usually yes	Yes
	Reoperation	No	No	Yes
	Death related to PF	No	No	Possibly yes
	Infection	No	Yes	Yes
	Sepsis	No	No	Yes
	Readmission	No	Yes/no	Yes/no
PPH [16]	Intra- or extraluminal hemorrhage following pancreatic resection			
	Timing and severity	Early (≤24 h) and mild	Early and severe OR late (>24 h) and mild	Late and severe
	Clinical condition	Well	Often well	Severely impaired, life-threatening
	Clinical consequence	Observation, CBC, US, ±CT	Observation, CBC, CT, angiography; requiring transfusion, ICU care, diagnostic or therapeutic endoscopy, embolization, or re-laparotomy for early bleeding	Angiography, CT, ±endoscopy or re-laparotomy, ICU care

DGE delayed gastric emptying, *PF* pancreatic fistula, *PPH* post-pancreatectomy hemorrhage, *NGT* nasogastric tube, *CBC* complete blood count, *US* ultrasound, *CT* computed tomography

frequently included in the resection as removal of this node facilitates exposure of the gastroduodenal artery (GDA). There is no consensus on a minimum number of nodes to be considered adequate for staging, but different groups have recommended numbers ranging from 11 to 17. Extended lymphadenectomy including aortocaval nodes has been investigated in prospective, randomized trials but has not been associated with a survival benefit. Extended lymphadenectomy has, however, been associated with increased morbidity [7, 18, 19]. Extended lymphadenectomy is therefore not recommended.

Consideration of the precise location of the tumor in the pancreatic head should be made to determine the area at highest risk for a positive margin. For tumors in the pancreatic head near the ampulla and those encroaching on the pancreatic neck, the common bile duct and pancreatic neck margins are at greatest risk for positivity; respectively, and should be assessed with frozen section intraoperatively. Intraoperative assessment of the pancreatic margin is not without controversy, however, as some studies suggest that re-resection does not change outcome, as margin status may be largely reflective of aggressive tumor biology [20]. Our general practice is to resect a positive pancreatic margin a single time. If persistently positive, it is unlikely that proceeding to more radical resection or total

pancreatectomy will alter oncologic outcomes. For uncinate process tumors, the retroperitoneal margin is at greatest risk; hence the SMA should be skeletonized to its adventitia. The superior mesenteric and portal veins should be completely mobilized off of the uncinate process first. The medial dissection is then extended to the adventitia of the SMA to maximize the retroperitoneal margin. If there is invasion of the SMV/PV, the SMA, or the hepatic artery by tumor, the area of vascular involvement should be left as the last point of attachment of the specimen so that proximal and distal control of the involved vessel can be achieved prior to reconstruction.

The most common reconstruction technique includes an end-to-side pancreaticojejunostomy (PJ) to the limb of proximal jejunum brought up in a retrocolic position, an end-to-side hepaticojejunostomy approximately 10 cm downstream from that, and an end-to-side gastrojejunostomy 20–30 cm downstream from that in a retro- or ante-colic position. Beyond these basic principles, multiple variations in technique of pancreatic resection and reconstruction have been investigated with the aim of reducing the incidence of postoperative complications.

Pylorus Preservation

PD with preservation of the pylorus, thereby dividing the proximal duodenum just distal to the pyloric ring, was popularized in the late 1970s. A duodenojejunostomy is then created, rather than a gastrojejunostomy (Fig. 11.2). Proposed benefits of this modification are improved digestive function and postoperative nutritional status, and decreased marginal ulceration. Concerns raised regarding pylorus preservation include increased incidence of DGE and inadequate clearance of peripyloric lymph nodes. Multiple randomized, prospective trials have been conducted comparing standard PD with pylorus-preserving PD (PPPD), the most recent of which are summarized in Table 11.2 [21–23]. In 2004, Tran and colleagues reported a prospective, randomized trial of 170 patients who underwent standard ($n=83$) or PPPD ($n=87$). The two groups were well matched for age, gender, tumor location, and stage. Two patients who were randomized to PPPD underwent standard PD due to suspicion of duodenal involvement and were included in the PPPD group for intention-to-treat analysis. There were no differences in median blood loss, operative time, DGE, or margin status between the groups. Postoperative weight loss was slightly greater in the PPPD group. On subset analysis of patients with adenocarcinoma, there were no differences in median disease-free or overall survival. The authors concluded that both techniques are equally effective.

In 2011, Kawai and colleagues compared PPPD with PD dividing the stomach just proximal to the pylorus, thereby preserving more stomach than what is typically done in classic PD. This was also a randomized, prospective

Table 11.2 Summary of recent randomized prospective studies evaluating pylorus-preserving vs. standard pancreaticoduodenectomy

Study		*N*	DGE (%)	*P*	≥Grade 3 Morbidity	*P*	Mortality	*P*
Mastumoto et al. [20]	PPPD	50	20	0.41	16 %	1.00	0	1.00
	SPD	50	12		14 %		0	
Kawai et al. [19]	PPPD	64	17	0.02	–	NS	0	0.99
	*SPD	66	5		–		1	
Tran et al. [21]	PPPD	87	23	0.80	–	NS	3	0.27
	SPD	83	22		–		6	

*In the SPD group in this study, the stomach was divided just proximal to the pylorus, thereby preserving more of the antrum than what is typically done in SPD

DGE delayed gastric emptying, *PPPD* pylorus-preserving pancreaticoduodenectomy, *SPD* standard pancreaticoduodenectomy, *NS* not significant

study and included 130 total patients (64 PPPD vs. 66 PD with pylorus resection) who were well matched for baseline characteristics. The authors found a statistically significant increase in DGE in the PPPD group (17.2 % vs. 4.5 %, $p=0.02$). There were no differences in other study endpoints including postoperative complications, mortality, quality of life, and nutritional status over a 6-month period following surgery. Oncologic outcomes were not reported. The authors concluded that resection of the pyloric ring may reduce DGE compared to PPPD.

Most recently, in 2014, Matsumoto reported 100 patients randomized to PPPD ($n=50$) or standard PD ($n=50$). The incidence of DGE was 20 % in the PPPD group compared to 12 % with standard PD, and this was not statistically significant ($p=0.41$). The study was powered to detect a 20 % difference in DGE rates. There were also no differences in the secondary endpoints, including postoperative complications, morbidity, long-term nutritional status, and diabetic status. Oncologic outcomes were not reported.

In summary, there is some evidence to suggest that pylorus preservation is associated with a higher incidence of DGE and there appears to be no difference in digestive function or nutritional status between the two techniques. While most of these studies concluded that the techniques are comparable, one must keep in mind that data on oncologic outcomes between PPPD and standard PD are very limited. Specifically, no studies reported the number of lymph nodes resected in PPPD vs. standard PD. At present, given the available data, both techniques are acceptable assuming adequate margin clearance can be achieved.

Braun Enteroenterostomy

A Braun enteroenterostomy is a side-to-side jejunal anastomosis between the afferent and efferent limbs of the gastro- or duodenojejunostomy. This technique was first described in 1893 as a means of reducing bile reflux, marginal ulceration, and afferent limb syndrome following distal gastrectomy for ulcer disease [24, 25]. In 2010, Hochwald and colleagues first reported the use of this technique in standard PD for reduction of DGE [25]. This was a retrospective study of 105 patients who underwent standard PD with ($n=70$) or without ($n=35$) a Braun enteroenterostomy. The Braun group had a 7 % incidence of clinically significant DGE compared to 31 % for the no-Braun group ($p=0.02$). The Braun group also experienced shorter length of hospital stay, and there was no difference in postoperative complications between the groups.

These findings were corroborated by a larger study in 2014. Xu et al. reported a series of 407 patients who underwent standard PD with ($n=206$) or without ($n=201$) Braun enteroenterostomy [26]. These patients were well matched for baseline characteristics. Braun enteroenterostomy was associated with decreased DGE (6.7 % vs. 26.9 %, $p<0.01$) with no difference in morbidity, and was the only independent predictor of DGE on multivariate analysis. While these data are encouraging, there are conflicting reports, and the use of Braun enteroenterostomy in PD has not been studied prospectively [27]. This technique does appear safe, however, and may reduce DGE, alkaline reflux, and marginal ulceration.

Pancreatic Anastomosis

As with DP, the most common source of major morbidity following PD is PF, occurring in approximately 10–30 % of cases. Pancreatic leaks in the setting of PD have even greater potential for morbidity than with DP, as in addition to sepsis, they can lead to delayed PPH and dehiscence of adjacent anastomoses. The major risk factors for PF include soft, or normal-textured pancreatic parenchyma and small (<3 mm) pancreatic duct diameter. Mortality associated with PF has decreased significantly, as tremendous advancements have been made in the management with early recognition and image-guided percutaneous drainage capabilities. Little success has been made in actually reducing the incidence of PF, however. Variations in surgical technique that have been investigated with the

aim of reducing PF include use of fibrin glue, omental patches, both internal and external stents, and pancreaticogastrostomy (PG), as an alternative to PJ. Of these techniques, the only two that have been demonstrated to reduce PF rates in high-quality, prospective studies are externalized stent placement and PG.

Externalized Pancreatic Duct Stent

The technique of externalized stent placement entails placing a small diameter catheter with multiple side-holes into the pancreatic duct, across the PJ anastomosis, and bringing it out through a small jejunostomy defect and through the abdominal wall to a drainage bag. The jejunostomy is reinforced with a purse string suture and the jejunal limb is tacked to the abdominal wall. Since the international consensus definition of PF was established in 2005, there have been three randomized, prospective trials comparing PJ with an externalized stent PJ with no stent [28–30]. The first was reported by Poon et al. in 2007 and included 120 patients, 60 in each group [30]. The authors found a decreased rate of CR-PF (ISGPS grade B/C) with externalized stent placement (3 % vs. 15 %; $p=0.03$). There were no differences in overall morbidity, reoperation rate, or in hospital mortality between the groups. The stented group had a shorter length of hospital stay (mean 17 ± 8 vs. 23 ± 12 days; $p=0.04$). The second study found conflicting results [28]. This was a smaller study and included only patients found to have a normal pancreas (without fibrosis based on preoperative MRI). Forty-five patients met the inclusion criteria and were randomized to PJ with ($n=23$) or without ($n=22$) an externalized stent. The rate of grade B PF was 22 % in the stented group vs. 27 % in the non-stented group and this was not statistically different. There were no grade C fistulae in either group. More recently, in 2012, Motoi and colleagues reported 93 patients who were randomized to PJ with ($n=47$) or without ($n=46$) an externalized stent. The authors again observed a decreased rate of CR-PF in the stented group (6 % vs. 2 %, $p=0.04$). Of note, approximately half of the patients in each group had a dilated (>3 mm) pancreatic duct. On subset analysis, external stent placement was not associated with PF in patients with dilated ducts.

In summary, external stent placement has been associated with low rates of CR-PF, but in the study that included only patients with soft glands, the rate of PF was still 22 %. Critics of this technique argue that it essentially gives all patients a PF, albeit a controlled one. Externalized stents were left in place for 2–6 weeks postoperatively in these studies, mandating prolonged postoperative care, which may not be feasible or preferable for some patients. This technique may have a role for reducing morbidity associated with PF in selected patients, but warrants further investigation given the conflicting results of the small studies that have been reported to date.

Pancreaticogastrostomy

PG is another surgical technique that has been investigated as a method of reducing PF. Four randomized, prospective trials of PG vs. PJ have been completed since 2005 [31–34]. The characteristics and results of these studies are summarized in Table 11.3. The first was published by Fernandez-Cruz in 2008 [31]. In this trial, 108 patients undergoing PD were randomized to PG ($n=53$) or PJ ($n=55$) at a single center in Spain. The PG technique was complicated and required pylorus preservation with preservation of the gastroepiploic vessels, gastric partitioning, and placement of a silastic stent sutured to the pancreatic duct for ducts <3 mm in diameter. The PJ technique was end-to-side duct-to-mucosa, also with stenting of small diameter ducts. The patients in the two groups were similar in terms of baseline characteristics including, age, BMI, pancreatic parenchymal consistency, duct diameter, and histologic diagnosis. The authors reported a rate of CR-PF of 3 % with PG vs. 18 % with PJ ($p<0.01$). There were also statistically significant decreases in intra-abdominal collections and overall 30-day morbidity with PG. There were no differences in operative time, blood loss, length of stay, postoperative

Table 11.3 Summary of recent randomized prospective studies evaluating pancreaticogastrostomy vs. pancreaticojejunostomy for reconstruction following pancreaticoduodenectomy

Study	Group	*N*	PF, *N* (%)	P	Morbidity, *N* (%)	*P*	Mortality, *N* (%)	*P*	LOS (days)	*P*
Fernandez-Cruz et al. [29]	PG	53	2 (3)	0.01	12 (23)	<0.01	0	NS	12±2	NS
	PJ	55	10 (18)		24 (44)		0		16±3	
Wellner et al. [32]	PG	59	6 (10)	0.78	–	NR	1	1.00	15 (7–135)	0.16
	PJ	57	7 (12)		–		1		17 (10–60)	
Figueras et al. [30]	PG	65	7 (11)	<0.01	41 63	0.78	3 (5)	1.00	12 (1–52)	0.72
	PJ	58	19 (33)		38 (66)		3 (5)		16 (6–55)	
Topal et al. [31]	PG	162	13 (8)	<0.01	–	NS	4 (3)	0.38	19 (14–25)	0.90

PF pancreatic fistula, *PG* pancreaticogastrostomy, *PJ* pancreaticojejunostomy, *LOS* length of stay, *NS* not significant

hemorrhage, or need for reoperation between the groups, and there was no postoperative mortality in either group. Despite the very low rate of PF in the PG group, this technique was never widely adopted. This is likely due to the complexity of the procedure, making it difficult to reproduce, and the need for pylorus preservation.

The next trial, reported by Wellner and colleagues in 2012, included 116 patients randomized to PG ($n=59$) vs. PJ ($n=57$) [34]. The PG technique in this study entailed invagination of the cut end of the pancreas into a posterior gastrostomy, with a double-layered anastomosis, performed via an anterior gastrostomy. The PJ was an end-to-side duct-to-mucosa anastomosis with a pancreatic duct stent that was exteriorized via a jejunopexy. The authors reported no difference in the primary endpoint of grade B/C PF between the groups (10 % PG vs. 12 % PJ, $p=0.78$). Operating time was shorter in the PG group (403 vs. 443 min; $p<0.01$), but there were no differences in any other secondary endpoints, including postoperative fluid collection, hemorrhage, reoperation, length of stay, or mortality. Clinically relevant DGE occurred more often with PG (27 % vs. 17 %), as did intraluminal bleeding (7 % vs. 2 %), but these differences were not statistically significant. The authors concluded that PG and PJ were equivalent.

Two additional studies published in 2013 demonstrated significantly reduced PF rates with PG vs. PJ [32, 33]. Topal and colleagues reported the largest of these [33]. A total of 329 patients were randomized to PG ($n=162$) or PJ ($n=162$). Randomization was performed intraoperatively and patients were stratified by pancreatic duct diameter (≤3 or >3 mm). PG and PJ were both performed by invagination. The rate of CR-PF was 20 % with PJ vs. 8 % with PG (odds ratio 2.86, 95 % CI 1.38–6.17; $p=0.002$). There was no difference in overall morbidity between the groups, but the PG group had a higher rate of DGE (15 % vs. 8 %; $p=0.04$) and lower rate of intra-abdominal abscess (6 % vs. 13 %; $p=0.03$). There were no differences in postoperative hemorrhage, reoperation, readmission, length of stay, or mortality.

While the majority of these studies, as well as several recent meta-analyses, conclude that PG is superior to PJ in terms of PF rate, PJ remains the most widely performed technique for pancreatic anastomosis. The data on PG need to be interpreted with caution as the technique of PJ varied significantly among the different studies, as did the associated PF rate. It is therefore not possible to definitively state that PG is superior. Additionally, more surgeons are trained to perform PJ and have more experience and a higher comfort level with that technique. It is clear, however, that PG is a safe and reasonable alternative to PJ, and it has a consistent, relatively low rate of CR-PF in recent studies.

Perioperative Care

In addition to surgical techniques, perioperative interventions also have a role in reducing morbidity associated with PD. This is particularly

true for patients with BRPC being treated with neoadjuvant therapy. These patients have a window of time before surgery during which nutritional status and medical comorbidities can be managed and optimized, and smoking and alcohol cessation can be achieved when necessary. Additionally, for patients presenting with jaundice, preoperative biliary drainage may be necessary and is discussed in Chap. 4. Additional perioperative measures that have been investigated as means of reducing PF and other morbidity particular to pancreatic resection include the use of somatostatin analogs, and the management of surgically placed drains.

Somatostatin Analogs

Somatostatin and somatostatin analogs are agents that act to decrease the volume of gastrointestinal secretions by binding to somatostatin receptors. Several of these agents, most commonly octreotide, have been investigated for their role in reducing the incidence of PF following pancreatic resection. A total of 19 randomized, prospective studies have been completed comparing somatostatin or an analog (octreotide or vapreotide) with placebo in the perioperative period in patients undergoing pancreatic resection [35]. These studies varied widely in sample size, definition of PF, technique of pancreatic anastomosis, use of prolonged bowel rest, and parenteral nutrition, and have shown conflicting results. Recently, several meta-analyses have been conducted and have uniformly concluded that the use of somatostatin analogs does not reduce the rate of CR-PF [27, 35, 36].

Pasireotide is a long-acting somatostatin analog with a 40-times greater affinity for the somatostatin receptor than octreotide. Evidence suggests that it has a broader binding ability than other somatostatin analogs and that it decreases intestinal secretions and trypsin release [37–40]. In theory it may then decrease both the volume of, and the likelihood of activation of, pancreatic secretions. In a study reported in 2014, patients undergoing pancreatic resection were randomized to pasireotide ($n=152$) vs. placebo ($n=148$) perioperatively [37]. A dose of drug or placebo was given subcutaneously twice daily starting on the morning of the day of surgery, and continuing for 7 days postoperatively. Patients were stratified by procedure (PD vs. DP) and by pancreatic duct diameter (>4 vs. ≤4 mm). The rate of CR-PF was 9 % in the pasireotide group vs. 21 % in the control group (RR 0.44, 95 % CI 0.25–0.95; $p<0.01$). This difference persisted regardless of procedure or pancreatic duct diameter. The rates of overall morbidity and readmissions were also significantly lower in the pasireotide group. Pasireotide is currently FDA-approved for use in Cushing's Disease and is under consideration for use for PF prevention.

Use of Drains

Another question that has prompted randomized, prospective studies is whether prophylactic intraperitoneal drains placed at the time of pancreatic resection impact the frequency or severity of postoperative complications, particularly PF. The first trial examining this question was performed at the Memorial Sloan-Kettering Cancer Center. One hundred and seventy nine patients undergoing PD or DP were randomized to routine intraperitoneal drainage with 7-mm closed-suction Jackson-Pratt (JP) drains (placed adjacent to pancreatic and hepatic anastomoses or transected pancreas) or no drains [41]. The majority of patients (78 %) underwent PD. No information was provided on pancreatic duct diameter or parenchymal consistency. The primary endpoint of the study was postoperative morbidity. There were no differences in the rates of overall or major morbidity, need for interventional radiologic intervention, need for reoperation, or length of stay between the groups. The rate of PF in the drained group was 12.5 % and by definition, was not measurable in the no-drain group. When the variables were combined, more patients in the drain group experienced intra-abdominal collection/abscess/fistula than in the no-drain group (22 % vs. 9 %, $p<0.02$). The authors concluded that routine placement of drains is not necessary and may be harmful.

In 2014, Van Buren et al. reported results of another randomized, prospective trial with a similar design. This was a multicenter trial conducted at 12 high-volume centers in the United States [42]. The authors hypothesized a 10 % difference in postoperative morbidity between the drain and no-drain groups, and aimed to enroll 752 patients (376 per group) to detect this difference with 80 % power. The study was stopped early due to an unacceptably high mortality rate of 12 % in patients who underwent PD without drains, compared to 3 % in the drain group. At the time the study was stopped, 137 patients had undergone PD with ($n=68$) or without ($n=69$) intraperitoneal drains. The number and type of drains placed was left to the discretion of the surgeon. Mean pancreatic duct diameter and percentage of patients with a soft gland were the same in each group (3.9 mm and 50 %; respectively). In addition to increased mortality, the no-drain group experienced a statistically significant higher incidence of overall morbidity, DGE, intra-abdominal collection, intra-abdominal abscess, need for postoperative percutaneous drain placement, and prolonged length of stay [42, 43]. Of the 8 patients who died postoperatively in the no-drain group, all but one died of complications related to PF (sepsis, multisystem organ failure, or intra-abdominal hemorrhage). When patients were stratified based on the author's risk score for PF (considering parenchymal consistency, pancreatic duct diameter, operative blood loss, and pathology), only those at moderate/high-risk appeared to benefit from drains. It was in this subset of patients that CR-PF (12.2 % vs. 29.5 %, $p=0.05$) and 90-day mortality were decreased [43].

Several conclusions can be drawn from these data. First of all, it is unlikely that the use of intraperitoneal drains is harmful. PF is defined by amylase content and volume of drain output, so patients without drains by definition cannot have a PF, thereby explaining why the drain group had a higher rate of PF in the first study. While there was no increase in intra-abdominal collection or abscess in the no-drain group, it may be that these patients were at low risk for development of PF. In the second study, it is clear that high-risk patients without drains experienced increased morbidity and mortality as a result of undrained pancreatic leaks. Routine use of intraperitoneal drains in selected patients at low risk for PF (firm gland, dilated pancreatic duct) is likely not necessary, but drains should be used judiciously in the majority of patients. This is especially true for patients who are likely to suffer major morbidity if they develop a pancreatic leak, such as those with adjacent vascular anastomoses. There is prospective data demonstrating that leaving drains in place for an excessive amount of time (>5 days) following pancreatic resection may be harmful, so drains should be removed as soon as is appropriate [44].

Summary

BRPC is a challenging disease that requires multimodality therapy for successful management. The role of the surgeon is to determine the optimal timing of resection and when feasible, to perform a margin-negative resection and regional lymphadenectomy with minimal morbidity. With more effective chemotherapy regimens and increasing data showing favorable outcomes, the utilization of neoadjuvant therapy for BRPC is likely to increase.

Data on surgical implications of neoadjuvant treatment are limited but growing. Ferrone et al. recently reported a series of 40 patients with locally advanced or BRPC who received neoadjuvant FOLFIRINOX with or without RT and went on to surgical exploration [1]. These patients were compared to 87 patients with resectable disease who underwent upfront surgical resection during the same time period. A margin-negative resection was achieved in 92 % of patients in the FOLFIRINOX group. Additionally, the patients in the FOLFIRINOX group had longer operative time (median 394 vs. 300 min; $p<0.01$), decreased blood loss (median 600 vs. 400 mL; $p<0.01$), decreased tumor size (median 2.5 vs. 3.2 cm), decrease rate of lymph node involvement (35 % vs. 79 %; $p<0.01$), decreased rates of lymphatic and perineural invasion (35 and 73 % vs. 70 and 95 %; $p<0.01$), and fewer postopera-

tive complications (36 % vs. 63 %; $p<0.01$). Surprisingly, no patients in the FOLFIRINOX group developed a CR-PF, compared to 22 % in the upfront surgery group ($p<0.01$). There were no differences in long-term oncologic outcomes between the groups.

These data are very encouraging and will hopefully be reproduced in future studies. Going forward, it is critical to prospectively document details of staging, neoadjuvant treatment, surgical technique, and perioperative care for patients with BRPC so that outcomes can continue to be improved.

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12 Is There a Role for Laparoscopic and/or Robotic Techniques for Borderline Resectable Tumors?

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer mortality in the United States, with an estimated 46,000 new cases and 40,000 of deaths in 2014 [1]. Few other cancers demonstrate a nearly 1:1 ratio of annual incidence and mortality. Surgery remains the only potential for cure but only 9 % of patients present with localized resectable disease, with most presenting with regional or metastatic disease [1, 2]. Despite improvements in diagnostic imaging, surgical techniques, and chemotherapeutic regimens, only small improvements in survival have been realized over the last three decades [3]. The estimated overall 5-year survival is 6 % for all stages, 24 % for localized disease, and 9 % for regional disease [1].

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Patients with localized PDA of the pancreatic head are classified into three categories: resectable, borderline resectable, or locally advanced (unresectable) [4–6]. This classification is based on the relationship of the tumor to the major regional vasculature, including the superior mesenteric vein/portal vein (SMV/PV), superior mesenteric artery (SMA), common hepatic artery (CHA), and the celiac axis (CA). Recent evidence suggests that patients with regional disease (borderline resectable or locally advanced) are able to achieve similar survival to patients with resectable cancer if negative margins are achieved at surgery, albeit at a slightly increased risk of morbidity and mortality [7–9]. This is usually accomplished in the setting of neoadjuvant chemotherapy (with or without radiation), which serves to increase the R0 resection potential, sterilize regional lymph node basins, and treat micro metastatic disease [10–14]. A recent meta-analysis demonstrated that one-third of patients with initially unresectable tumors respond to neoadjuvant therapy and eventually undergo resection, with comparable survival to patients with initially resectable tumors [15].

Minimally invasive (MI) approaches are being increasingly applied to the treatment of PDA in an effort to reduce morbidity. Although lacking widespread adoption, several single and multi-institutional series have confirmed the safety and feasibility of this approach, particularly in carefully selected patients. However, the

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use of MI platforms to treat borderline resectable or locally advanced tumors remains even more controversial. This chapter will highlight the available evidence and outcomes of MI techniques on this subgroup of patients with advanced disease.

Minimally Invasive Pancreatectomy for Resectable Pancreatic Cancer

Despite the advantages provided by MI surgery, its acceptance in pancreatic surgery—particularly for PDA—has lagged behind other fields [16, 17]. The reasons for this are multifactorial and include the complex retroperitoneal anatomy of the head of the pancreas, the technically challenging reconstructions associated with the pancreaticoduodenectomy (PD), and the lack of randomized controlled trials. Despite this, multiple reports have established the safety and feasibility of laparoscopic, and more recently, robotic-assisted pancreatectomy in well-selected patients at large centers of experience.

Laparoscopic Pancreatectomy for Resectable PDA

Compared to laparoscopic pancreaticoduodenectomy (LPD), the laparoscopic distal pancreatectomy (LDP) has been more extensively examined due to its purely ablative nature. Multiple large retrospective series have now demonstrated its safety, efficacy, and potential benefit when compared to its open counterpart, even when performed for PDA [18–27]. In the largest multi-institutional comparative analysis to date, Kooby et al. retrospectively matched 200 patients that underwent open distal pancreatectomy (ODP) to 142 patients that underwent LDP [27]. Laparoscopic resections were associated with less blood loss (EBL) (357 vs. 588 mL; $p<0.001$), a lower rate of splenectomy (70 % vs. 88 %; $p<0.001$), and shorter hospital length of stay (LOS) (6 vs. 9 days; $p<0.001$). There were fewer overall complications in the LDP group (40 % vs. 57 %; $p=0.003$) and a lower rate of wound infections (5 % vs. 15 %; $p=0.004$). There were no differences in overall pancreatic fistula rate or clinically significant (Grade B/C) fistula rate, as defined by the International Study Group of Pancreatic Fistula (ISGPF) [28]. On multivariate analysis, LDP was an independent predictor for EBL of less than 500 mL, reduced morbidity, and LOS less than 7 days. In a follow-up comparison of ODP to LDP for PDA patients, this multi-institutional consortium compared 212 ODP patients to 23 non-matched LDP patients [29]. Again, LDP was associated with lower EBL (422 vs. 790 mL; $p=0.04$) and shorter LOS (7 vs. 11 days; $p=0.03$). When matched in 3:1 fashion (70 ODP vs. 23 LDP) based on age, American Society of Anesthesiologists (ASA) class, and tumor size, LDP was associated with lower EBL and shorter LOS, although these differences did not reach statistical significance. Importantly, the method of resection did not impact margin status or total lymph node harvest, and overall survival at a median follow-up of 10 months was similar between both groups. The authors concluded that LDP was at least equivalent to ODP with regard to short-term operative and oncologic outcomes, and therefore a reasonable approach to appropriately selected patients with PDA. These studies have contributed to a paradigm shift in the management of tumors of the pancreatic body and tail, and consequently, MI DP is the preferred approach for many high volume pancreas surgeons with expertise in laparoscopy. Table 12.1 summarizes other large series comparing LDP to ODP.

In contrast to DP, MI approaches for PD have been slow to develop despite being first reported nearly two decades ago [30–32]. The past 5 years, however, have witnessed renewed interest in MI PD, fueled by reports of feasibility and the prospect of reducing the substantial morbidity (up to 50 %) associated with OPD [33, 34]. Croome et al. recently published the largest comparative series between LPD and open PD (OPD) for patients with PDA [35]. Over a 5-year period, a total of 108 patients underwent LPD and 214

Table 12.1 Summary of selected studies comparing laparoscopic and open distal pancreatectomy

	N		Malignancy (%)		Operative time (min)		EBL (mL)		LOS (days)		Overall morbidity (%)		30-day mortality (%)		R0 resection (%)		Lymph node harvest (mean)	
Author	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open
DiNorcia [18]	71	192	**13**	39	**250**	270	**150**	900	**5**	6	**28**	44	0	1	**97**	87	6	8
Jayaraman [20]	100	100	**17**	47	**195**	160	**175**	300	**5**	6	26	33	0	0	97	98	6	5
Kim [21]	93	35	0	0	195	190	NR	NR	**10**	16	25	29	NR	NR	NR	NR	NR	NR
Vijan [26]	100	100	23	23	214	208	**171**	519	**6**	9	34	29	3	1	NR	NR	NR	NR
Kooby [27]	142	200	38	42	230	216	**357**	588	**6**	9	**40**	57	0	1	92	93	NR	NR
Kooby [29]	23	70	100	100	238	216	422	751	7	9	NR	NR	0	2	74	66	14	12

Lap laparoscopic, *NR* not reported
Bold $p < 0.05$

Table 12.2 Summary of studies comparing laparoscopic to open pancreaticoduodenectomy

Author	*N*		Malignancy (%)		Operative time (min)		EBL (mL)		LOS (days)		R0 resection (%)		Lymph node harvest (mean)	
	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open
Asbun [39]	53	215	75	67	**541**	401	**195**	1032	**8**	12	95	83	**23**	17
Kuroki [40]	20	31	70	74	657	555	**377**	1510	NR	NR	NR	NR	14	26
Croome [35]	108	214	100	100	379	388	**492**	867	**6**	9	78	77	21	20

Lap laparoscopic, *NR* not reported
Bold $p<0.05$

underwent OPD. The authors found that LPD was associated with a lower EBL (492 vs. 867 mL; $p<0.001$), lower rates of delayed gastric emptying (11 % vs. 26 %; $p=0.03$), and a shorter LOS (6 vs. 9 days; $p<0.001$), with no difference in R0 resection rates, overall complication rates, or postoperative pancreatic fistulae. Importantly, LPD was associated with a significantly shorter time period from surgery to the initiation of adjuvant chemotherapy (48 days vs. 59 days; $p=0.001$); fewer long delays (>8 weeks) between time of surgery and initiation of chemotherapy (27 % vs. 41 %; $p=0.01$); and lower rates of patients failing to receive chemotherapy altogether or within 90 days of surgery (5 % vs. 12 %; $p=0.04$). There was no difference in overall survival, but LPD was associated with a longer progression-free survival. Although limited by its retrospective nature and small numbers, this comparison offers important insights into the potential benefits of MI pancreatectomy. PD is associated with significant morbidity and prolonged convalescence that may preclude the receipt of any adjuvant chemotherapy or its full scheduled dose [36]. The potential for MI surgery to reduce the morbidity associated with PD is important since this would increase the number of patients that could derive potential benefit from postoperative chemotherapy, particularly as potentially effective regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel are being evaluated in the adjuvant setting [37, 38]. To date, only three studies have compared LPD to OPD [35, 39, 40], and these are summarized in Table 12.2. Although some of these series are not exclusive to PDA patients, their outcomes suggest that the LPD can be performed with equivalent short-term oncologic outcomes, less EBL, and shorter LOS (at the expense of slightly longer operative times) compared to OPD in select patient cohorts.

Robotic-Assisted Pancreatectomy for Resectable PDA

The inherent visual and ergonomic limitations of laparoscopy have played a major role in the development of robotic surgery, which allows surgeons to perform advanced laparoscopic procedures with greater ease. Advantages include articulating instruments that re-create the seven-degrees of freedom of the human wrist, three-dimensional high-definition view of the operative field, and complex algorithms that minimize physiologic tremor. These features allow for precise dissection and intracorporeal suturing, thus expanding the scope and complexity of procedures that can be performed in MI fashion. Disadvantages include high cost, loss of haptic feedback, the inability to operate in multiple fields, and the need for a skilled bedside assistant. The lack of haptic feedback is generally overcome by the enhanced, three-dimensional visualization, which allows the operating surgeon to use visual cues as a compensatory mechanism [41]. The platform has controls and ergonomics that closely mimic the movements of open surgery, and appears to shorten the learning curve for complex cases compared to conventional

laparoscopy. This should allow a greater number of surgeons to perform complex pancreatic resections, and—by extension—increase the number of patients treated by MI pancreatectomy.

The first report of robotic-assisted pancreatectomy was by Guilianotti et al. in 2003 [42]. Since then, various reports have emerged to confirm the safety and feasibility of this platform. In the largest single-institutional experience of 250 consecutive robotic-assisted pancreatic resections [43], the authors at the University of Pittsburgh examined 132 patients that underwent robotic pancreaticoduodenectomy (RPD) (80 % were for malignancy of which 41 % were resectable PDA) and found the outcomes comparable to large historic retrospective series of OPD [3, 44]. For the malignant cohort, R0 resection was achieved in 88% of patients with a median of 19 resected lymph nodes. Similarly, for the 83 patients that underwent robotic distal pancreatectomy (RDP) (72 % for malignancy of which 37 % were resectable PDA), R0 resection was achieved in 97 % of patients with a median of 14 lymph nodes resected. No long-term survival data were available due to a short follow-up period. In a separate propensity score-matched analysis of 34 ODP and 28 MI DP (robotic and laparoscopic) for resectable PDA, the same group found short-term oncologic outcomes (R0 and lymph node harvest) and disease-specific survival to be equivalent [45]. Finally, in a retrospective comparison of 94 LDPs and 30 RDPs, the same group noted several advantages to the robotic approach including significantly reduced operative times, EBL, and conversion rates [46]. Furthermore, RDP was associated with superior short-term oncologic outcomes in patients with PDA, including a lower rate of microscopically positive margins and a greater lymph node harvest. Table 12.3 highlights some of the major series reporting on RPD to date. Similar to the LPD series, RPD seems to be associated with reduced EBL and LOS at the expense of longer operative times. These data must be viewed with caution since most of these series, particularly for PD, are limited by their retrospective nature, small numbers, and inherent selection bias. Conversely, many if not all of these series represent surgeons working through their initial learning curve. Future reports will focus on outcomes beyond this implementation phase, allowing for a more robust assessment of any benefits to this costly platform.

Minimally Invasive Approaches to Borderline Resectable Pancreatic Cancer

Challenges

Whereas the application of MI surgery to benign and resectable malignant disease is slowly expanding, its utility for borderline resectable and locally advanced tumors poses a unique set of challenges. The potential for catastrophic hemorrhage, coupled to oncologic concern for margin clearance, has contributed to a paucity of reported outcomes on this subset of patients. Moreover, borderline resectable tumors are usually larger in size and associated with increased rates of preoperative chemotherapy or chemoradiotherapy administration—factors that potentially contribute to more difficult resections. Additionally, the lack of available data on the cost-benefit ratio for MI PD for benign disease and resectable cancers translates to reduced enthusiasm to apply the MI platforms to the more complex borderline resectable tumors.

From a technical standpoint, it may appear that the robotic platform is better suited for vascular resections and reconstructions than conventional laparoscopy due to the stereotactic vision, stability, and articulating instruments. Conversely, a distinct disadvantage of this bulky platform is the difficulty and challenge in converting a case to laparotomy, particularly in the setting of bleeding. A robotic conversion is invariably slower—and potentially more hazardous—compared to laparoscopy, and mandates the presence of a bedside assistant experienced in laparoscopy, who can grasp and provide temporary control of hemorrhage using conventional laparoscopic techniques. Due to these safety concerns, centers that have reported on MI pancreatic resections for borderline resectable tumors have only done so after garnering a substantial experience in benign and resectable pancreatic tumors.

Table 12.3 Summary of selected studies reporting on robotic pancreaticoduodenectomy

	N		Malignancy (%)		Operative time (min)		EBL (mL)		LOS (days)		Overall Morbidity (%)		30-day mortality (%)		R0 resection (%)		Lymph node harvest (mean)	
Author	Rob	Open	Rob	Open	Rob	Open	Rob	Open	Rob	Open	Rob	Open	Rob	Open	Rob	Open	Rob	Open
Buchs [58]	44	39	75	69	**444**	559	**387**	827	13	15	36	49	4.5	2.6	91	81	**17**	11
Lai [59]	20	67	75	79	**492**	265	**247**	775	**14**	26	50	50	0	3	73	64	10	10
Chalikonda [60]	30	30	46[a]	46[a]	**476**	366	485	775	**10**	13	30	43	4	0	**100**	87	13	12
Giulianotti [61]	60	–	75	–	421	–	394	–	22	–	NR	NR	3	–	92	–	18	–
Zureikat [43]	132	–	80	–	527	–	350	–	10	–	63	–	1.5	–	88	–	19	–

Rob robotic, *NR* not reported
[a]Only reported for PDA
Bold $p < 0.05$

Published Outcomes

To date, only four series have published outcomes on vascular resections for borderline resectable or locally advanced tumors [47–50]. These reports emanate from tertiary care centers with large experiences in MI and pancreatic surgery. Additionally, all of the authors have previously published extensively on MI pancreas resections for resectable PDA prior to attempting more advanced vascular resections. Three scenarios of vascular resections have been reported in the MI literature: the first is a PD with tangential venous resection using a linear stapler or a venectomy that requires patch venorraphy; the second is PD or DP with venous resection of the SMV/PV or splenoportal confluence with primary end-to-end reconstruction or graft interposition (internal jugular or left renal vein); and the third is the modified Appleby procedure, which requires resection of the celiac trunk in the setting of a locally advanced (T4) pancreatic body tumor that involves the celiac branches proximal to the takeoff of the GDA.

Kendrick and Sclabas from the Mayo Clinic reported on 11 patients that underwent venous resection during LPD [49]. Nine of the 11 cases were performed for PDA. One patient was converted to an open approach. Ten of the 11 patients underwent tangential venous resection and 1 patient underwent segmental resection. Patients undergoing partial venous resection were reconstructed by primary venorrhaphy ($n=4$), patch venorrhaphy ($n=4$), or tangential stapling ($n=2$). A single patient underwent segmental venous resection with reconstruction using a left renal vein interposition graft. Median operative time, mesoportal clamp time, and EBL were 400 min, 35 min, and 500 mL, respectively. The R0 resection rate was not compromised (90 %). Overall morbidity was 55 % with no in-hospital or 30-day mortality, and median LOS was 7 days. These results were comparable to some of the larger existing series of major venous resection during open PD [7, 51].

The Mayo Clinic group expanded on these preliminary data and published a retrospective study comparing short- and long-term outcomes in patients who underwent major venous resection during open ($n=58$) and laparoscopic ($n=31$) PD [48]. The laparoscopic approach was associated with less operative blood loss (842 vs. 1452 mL; $p<0.001$), a higher R0 resection rate (94 % vs. 76 %; $p=0.038$), and a greater lymph node harvest (20 vs. 16 lymph nodes; $p=0.01$). Expectantly, patients undergoing open procedures had a higher frequency of segmental venous resections requiring primary end-to-end anastomosis or interposition graft reconstruction, whereas partial venous resections were more frequent in the laparoscopic cohort ($p<0.05$). The laparoscopic group had a shorter hospital length of stay (6 vs. 9 days; $p=0.006$). There was no difference in the rate of overall or severe (Clavien-Dindo grade ≥III) complications [52], and 90-day mortality was similar in both groups. There was a trend toward more ISGPF Grade B/C pancreatic fistulas in the laparoscopic group (16 % vs. 5 %), but this did not reach statistical significance ($p=0.09$). There appeared to be a trend toward improved long-term survival in the laparoscopic group, but this did not reach statistical significance. To date, this report remains the largest experience of LPD for borderline resectable tumors. The results are impressive and demonstrate that MI PD with venous resection is safe and feasible when performed by a talented surgeon with robust experience in pancreatic surgery and advanced laparoscopy. Although LPD was associated with beneficial outcomes, definitive conclusions cannot be made given the baseline dissimilarities between the groups with regards to complexity of operations performed.

Two other small series have reported on MI pancreatectomy requiring vascular resections. Giulianotti et al. reported on 5 patients that underwent robotic pancreatectomy [50]. Two patients underwent RPD with portal vein resection (1 tangential SMV/PV resection using an endovascular stapler, 1 PTFE patch venorraphy), 2 patients underwent RDP with celiac axis resection (modified Appleby operation), and 1 patient underwent RDP with portal vein resection (PTFE patch venorraphy). Notably, a 7 cm laparotomy was performed in the 2 patients requiring patch venorraphy. There were no postoperative deaths, and 4 patients received R0 resections. Boggi et al. reported on a series of 34 patients that

underwent RPD, of which three patients required segmental resections of the SMV/PV, but no specific data on these patients is provided [47].

Authors' Approach to Robotic Pancreatectomy for Borderline Resectable and Locally Advanced Tumors

Patient Selection

The previously reported advantages of the robotic platform have made it the preferred MI approach at our institution. As with any surgical platform, patient selection remains central to successful implementation. At our institution, preoperative planning includes a triphasic (pancreatic protocol) CT scan of the abdomen and pelvis as well as endoscopic ultrasound (EUS). The combination of these two modalities has proven highly predictive of the ability to achieve an R0 resection in a validated model [53]. Additionally, patients with borderline resectable/locally advanced disease undergo treatment with neoadjuvant chemotherapy (with or without radiation depending on the available protocols), in order to maximize the potential for R0 resection. Importantly, RPD, RDP, and the robotic-modified Appelby procedure are performed exclusively by surgeons experienced in both open and robotic pancreatic resections and venous reconstruction.

Technique

Our technique for a standard (resectable lesion) RPD and RDP has been previously described [54–56]. Typical port placement is depicted in Fig. 12.1. For a borderline resectable RPD with anticipated vein resection, we employ an "artery-first" approach, staying to the left of the

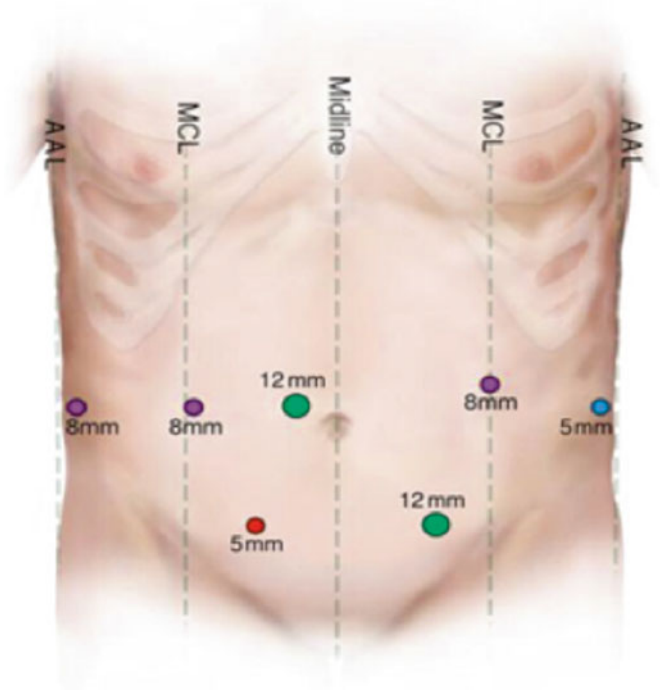

Fig. 12.1 Port placement for robotic-assisted pancreaticoduodenectomy. A 12 mm camera port is placed to the right and superior to the umbilicus. Eight millimeter robotic ports are placed in the left midclavicular line (Arm 1), right midclavicular line (Arm 2), and right anterior axillary line (Arm 3). A self-retaining liver retractor is placed through a 5 mm port in the left anterior axillary line. Two assistant ports are placed below the umbilicus on either side of the midline at the midpoint of the symphysis pubis and umbilicus. The 12 mm assistant port is enlarged and serves as the specimen extraction site

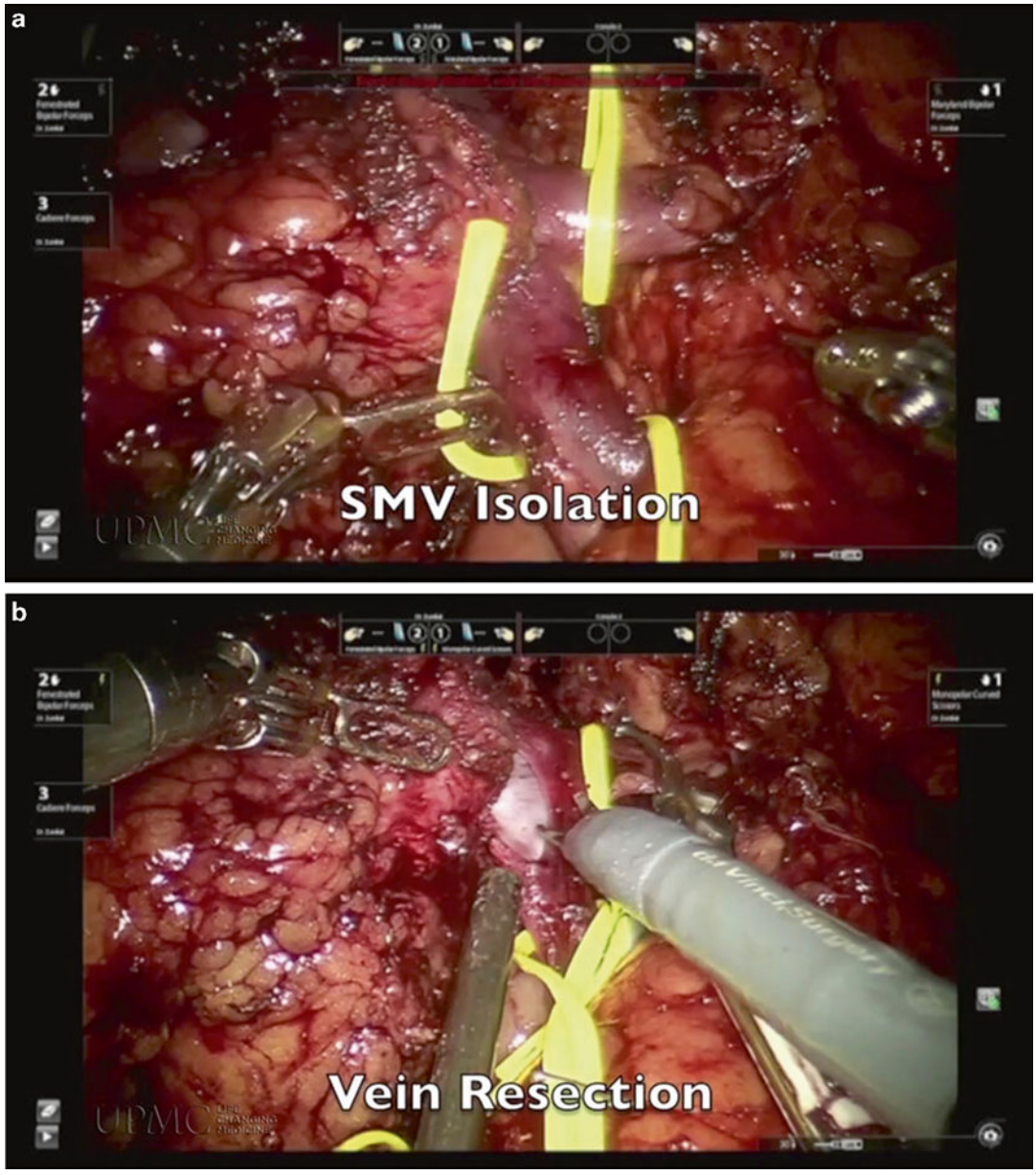

Fig. 12.2 Robotic pancreaticoduodenectomy with tangential resection of SMV/PV and patch venoplasty for a borderline resectable tumor at the splenoportal confluence. (**a**) Isolation of the SMV, PV, and splenic vein at the level of the splenoportal confluence. (**b**) After vascular occlusion, a partial venectomy is created with robotic endoshears. (**c**) A bovine pericardial patch is used for patch venoplasty and is sutured in place with 5-0 polypropelene. (**d**) Completed patch venoplasty

SMV/PV axis, working from caudad to cephalad [57]. This serves to clear all the tissue around the SMA in 180° fashion on its right side, such that the only remaining attachment of the tumor is its venous involvement. At this stage, the extent of venous resection is determined. If abutment is minimal, we perform a tangential resection with a stapler. If abutment is moderate (45–180° of involvement), we perform a partial venectomy with bovine pericardial patch venorraphy. Next, we achieve vascular control of the SMV, PV, and splenic vein (Fig. 12.2a) with

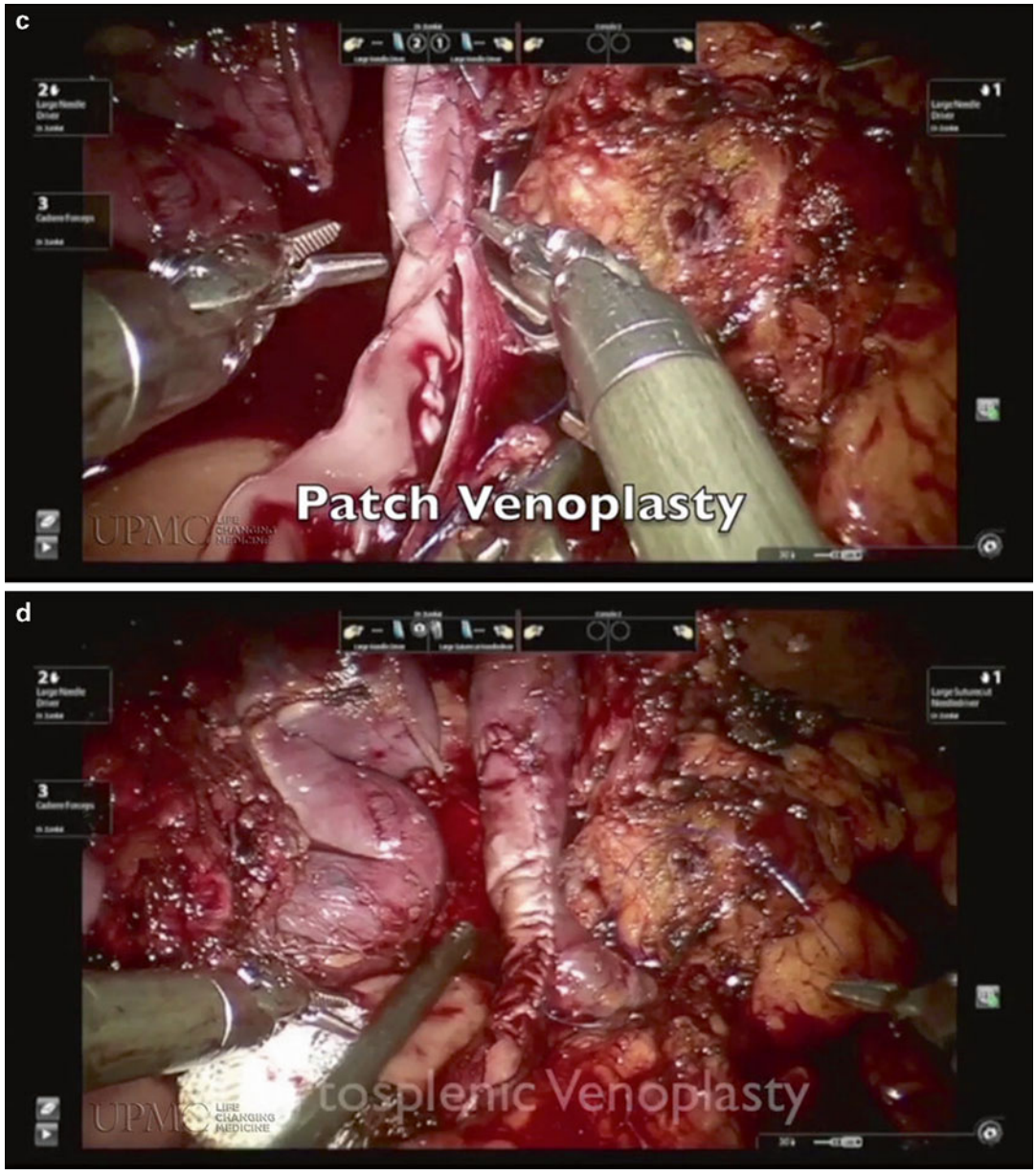

Fig. 12.2 (continued)

vessel loops, the patient is heparinized with an unfractionated bolus, and laparoscopic vascular bulldog clamps are placed across the three venous tributaries by the bedside assistant. Next, tangential resection or partial venectomy is performed (Fig. 12.2b). The venotomy is closed primarily with 5-0 non-absorbable polypropylene sutures or by patch venorraphy using bovine pericardium (Fig. 12.2c, d). We have elected not to approach tumors involving more than 180° of the SMV/portal vein using the robotic approach, preferring thus far to perform these cases in open fashion due to the potential of needing an internal jugular venous graft interposition.

Typical port placement for the robotic modified Appleby procedure is depicted in Fig. 12.3.

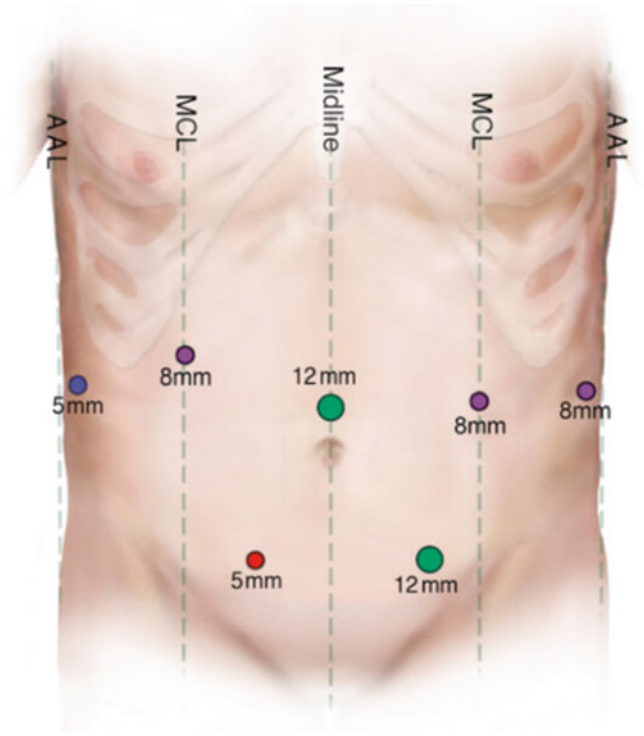

Fig. 12.3 Port placement for robotic-assisted distal pancreatectomy and modified Appelby procedure. A 12 mm camera port is placed in the subra-umbilical midline. Eight millimeter robotic ports are placed in the left midclavicular line (Arm 1), right midclavicular line (Arm 2), and left anterior axillary line (Arm 3). A self-retaining liver retractor is placed through a 5 mm port in the right anterior axillary line. Two assistant ports are placed below the umbilicus on either side of the midline at the midpoint of the symphysis pubis and umbilicus. The 12 mm assistant port is enlarged and serves as the specimen extraction site

We begin with opening the lesser omentum and exposing the CHA at the superior border of the pancreas. We trace it distally and expose the takeoff of the gastroduodenal artery (GDA). We temporarily test-occlude the CHA with a laparoscopic bulldog clamp and use ultrasound to confirm that adequate collateral arterial blood flow is present in both lobes of the liver via retrograde GDA flow from the SMA. Next, we divide the gastrocolic ligament and enter the lesser sac, ligating the short gastric vessels and clearing the anterior surface of the pancreas. The insertion of the transverse mesocolon at the inferior border of the pancreas is divided to enter the retropancreatic plane, generally at the level of the SMV, taking care to identify the splenoportal confluence while creating a tunnel underneath the pancreatic neck. We then sequentially transect the pancreatic neck and CHA using an endovascular stapler (Fig. 12.4a). Next, we establish proximal and distal control of the SMV/PV at the splenoportal confluence and transect the splenic vein at or just distal to the SMV/PV junction (Fig. 12.4b). If there is tumor involvement of the SMV/PV, we will perform a partial vein resection. We then continue our dissection on the anterior surface of the SMA and trace it proximally to the aorta, taking the celiac plexus and isolating the celiac trunk. Our dissection is aided with the use of a robotic ultrasound probe, which allows visualization of the origins of the SMA and celiac axis (Fig. 12.4c). We then divide the left gastric artery just distal to its takeoff using an endovascular stapler. With the celiac artery completely isolated, we transect it at its origin using the endovascular stapler (Fig. 12.4d). The dissection then proceeds laterally, elevating the pancreas and spleen off of the retroperitoneum.

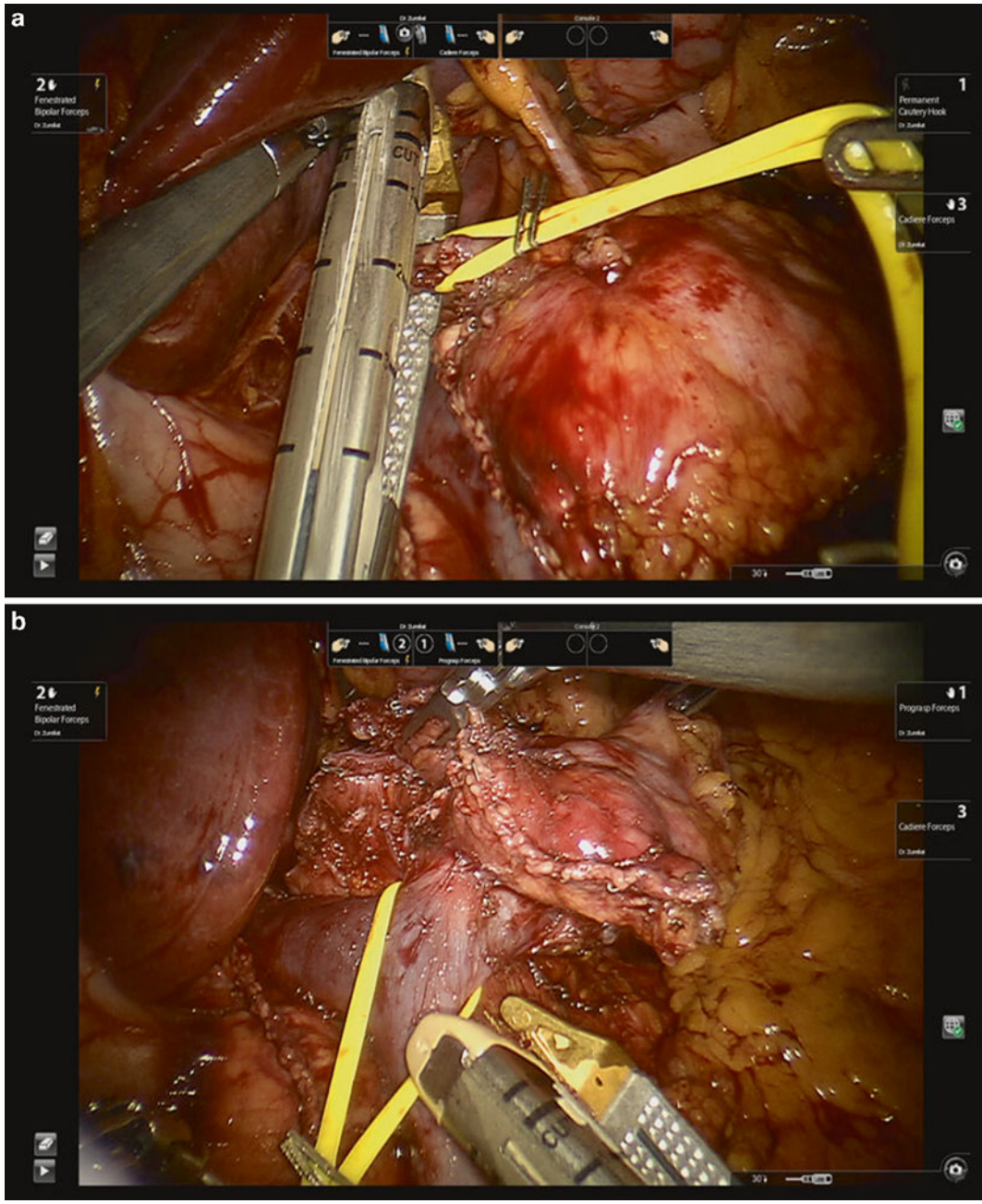

Fig. 12.4 Robotic modified Appelby procedure for a locally advanced (T4) tumor involving the celiac branches. Importantly, the celiac trunk and the GDA are not involved, allowing resections of the neck, body, tail of the pancreas with en bloc resection of the celiac trunk. (**a**) The common hepatic artery is transected with a linear stapler after ensuring adequate retrograde flow through the GDA. (**b**) The splenic vein is transected at the splenoportal confluence after division of the pancreas at the level of the pancreatic neck. (**c**) Robotic-assisted ultrasound is used to assist with dissection along the SMA and aiding identification of the SMA and celiac axis origins (*arrow*). (**d**) The celiac trunk (uninvolved with tumor) is transected at its origin

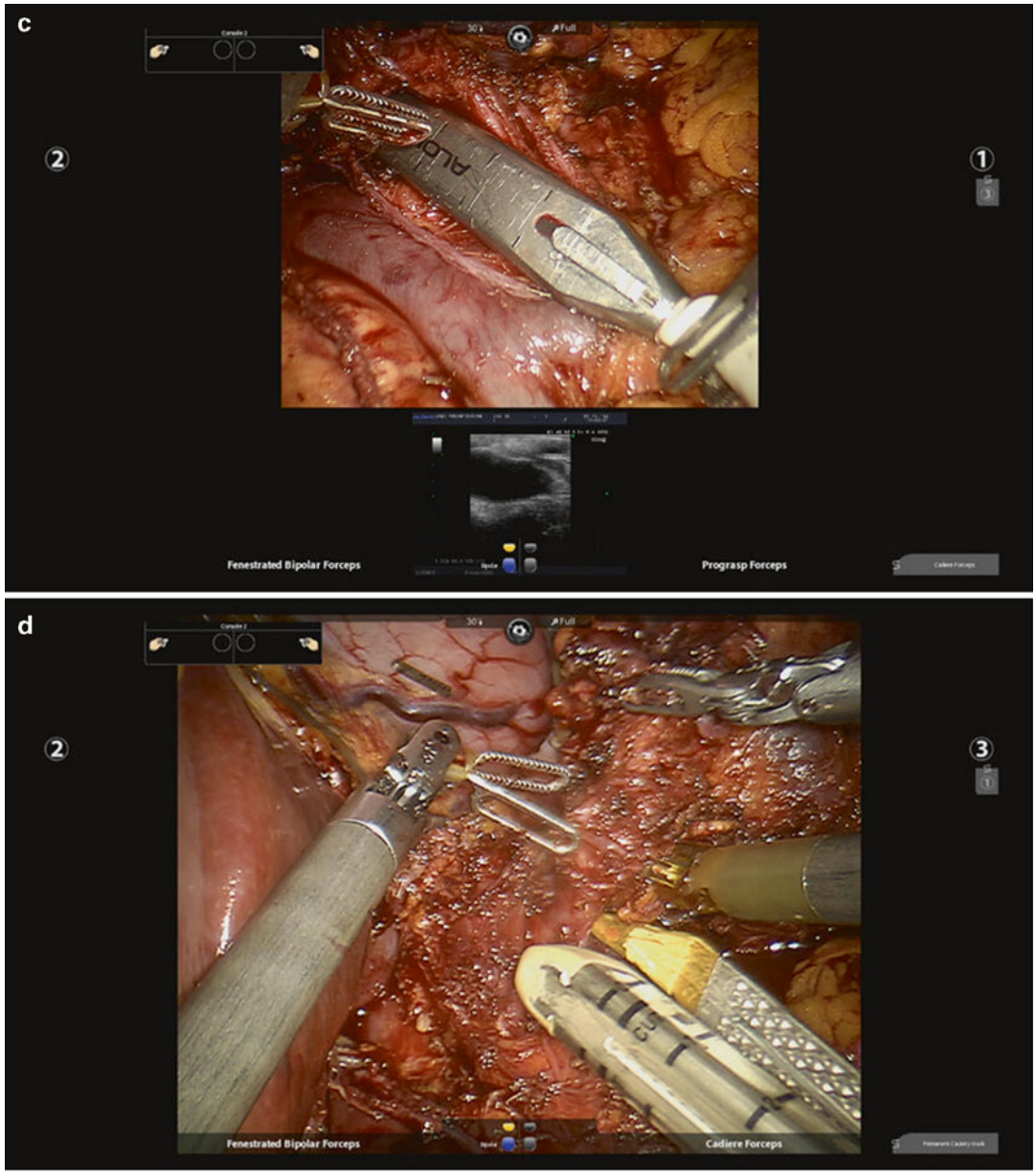

Fig. 12.4 (continued)

Outcomes

At the University of Pittsburgh, we have performed 27 RPD requiring partial venous resection, 7 robotic modified Appleby procedures, and 3 RDP with partial PV resection (unpublished data). The RPD cohort included PDA in 21 patients (78 %), cholangiocarcinoma ($n=2$), ampullary adenocarcinoma ($n=2$), and 1 patient each with acinar cell carcinoma and adenosquamous cell carcinoma. Mean operative time was 436 min and EBL was 466 mL. Average tumor size was approximately 3 cm. Twenty-three (85 %) underwent tangential PV/SMV resection with primary repair or stapled closure and 4 patients (15 %) underwent patch venoplasty.

Margin negative (R0) resection was achieved in 20 patients (74 %) and an average of 34 lymph nodes were harvested. Two patients (7 %) required conversion to laparotomy. Overall complication rate was 52 %, with an 11 % Grade B/C pancreatic fistula rate. Two patients died within 90 days of surgery (7 %). Five patients (19 %) required transfusion of blood products in the intraoperative or immediate postoperative period. Overall hospital LOS was 8 days and the readmission rate was 44 %.

Regarding the robotic Appelby cohort, locally advanced (T4 tumors involving the celiac axis) PDA was present in all 7 patients. PDA was also present in all 3 patients that required RDP with tangential venous resection. For the entire 10 patient cohort of RDP with major vascular resection, mean operative time was 291 min and EBL was 392 mL. No procedures required conversion. Margin negative (R0) resection was achieved in 9 out of 10 patients with a mean of 24 lymph nodes harvested. Overall hospital LOS was 11 days and the readmission rate was 50 %. Six patients had complications and only one patient required transfusion. There were no 30- or 90-day mortalities.

Similar to the Mayo Clinic experience, these results indicate that MI pancreatectomy with concomitant vascular resections can be performed with outcomes similar to open cohorts. However, these outcomes are predicated on a large prior experience of resectable cases, careful patient selection, and a two attending approach to ensure patient safety and oncologic efficacy. These preliminary data are promising but need to be validated by larger cohorts, long-term follow-up, and robust cost analysis.

Conclusion

Currently, the role of MI approaches for borderline resectable and locally advanced pancreatic cancer remains controversial. Data is limited to a handful of small single-institutional retrospective studies. These reports indicate that short-term operative and oncologic outcomes (R0 resection and lymph node harvest) are not inferior to historic controls, but data regarding long-term oncologic efficacy is lacking. Thus, despite the reported safety and feasibility in existing studies, MI surgery should not be advocated for this subset of advanced disease, unless it is performed at high volume hepatopancreatobiliary centers by surgeons who possess extensive prior experience in both open and MI pancreatic surgery.

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The Role and Techniques of Vascular Resection

13

Mark J. Truty

Introduction

A "removable" tumor is one that can be surgically separated from a patient. A "resectable" tumor, in contrast, is one that can be removed within specific anatomic, biologic, and conditional constraints [1, 2]. Within this rubric, a borderline resectable tumor is one which can be surgically removed, but at "high risk" with respect to one or more of these constraints.

Although most patients presenting with a new diagnosis of pancreatic adenocarcinoma have various combinations of anatomic, biologic, and conditional factors that may influence the appropriate application of surgery, most of the literature and focus has been on anatomy alone. Based on specific imaging criteria, pancreatic cancers are classified according to their locoregional tumor extent and their involvement of critical vascular structures as anatomically resectable, anatomically borderline, or anatomically locally advanced/unresectable [3, 4]. Patients with anatomically borderline features have a higher risk of a positive margin resection in the absence of vascular resection. Furthermore, many of these patients with anatomically advanced cancers also have occult disseminated disease with a high risk for early recurrence making them biologically borderline, as well as conditionally borderline risk factors which place them at high risk for failure to receive recommended adjuvant therapy when surgery is used as primary therapy. A strong rationale therefore exists for the administration of preoperative therapy in such patients prior to resection.

When discussing the benefits of surgical resection for patients with pancreatic cancer, which is the only known modality that offers the possibility of cure or long-term survival (albeit in a small fraction of patients), one must assess the added benefit of resection compared to nonoperative therapies [5, 6]. Historically, comparisons have been made to patients receiving palliative procedures and supportive care. However, in light of advances in modern nonoperative treatment, this is no longer a valid comparison. Several recent studies looking specifically at patients with locally unresectable pancreatic cancer offer insight into what the modern comparison outcomes should be. Such patients who are treated with modern extended systemic chemotherapeutics followed by locoregional chemoradiation have been reported to live up to 18 months without surgery [7–10]. These nonoperative survival statistics rival those reported in many large surgery-first series. This suggests that in order to consider resection as a relevant modality for these patients we need to further improve upon this new thresh-

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old in long-term mortality—presumably using a combined multimodality approach [11, 12].

There is convincing scientific evidence that for the majority of patients with pancreatic cancer, the disease is systemic at diagnosis [13, 14]. For this reason, and given that "curative" surgical outcomes have had minimal improvements over the past few decades, a significant nihilism has developed and many patients are being denied resection as a potential life-extending modality as a result [15]. However, there does exist a significant proportion of patients that exhibit a "locally dominant phenotype," in that such cancers behave more in a locally invasive nature rather than a diffusely metastatic biology, perhaps due to divergent mutational evolution. Patients with locally dominant disease may truly benefit from aggressive locoregional surgical therapies. The best evidence for this stems from results of several autopsy studies and observational series of patients with locally advanced unresectable cancers. In these reports approximately 10–30 % of patients presenting with unresectable but localized disease ultimately died without evidence of metastatic disease [16–19]. Although a subset of patients may have this locally dominant phenotype, distant disease remains the most common pattern of recurrence or progression among patients who present with localized pancreatic cancer. The utilization of systemic therapies for all patients is therefore rational.

Elsewhere in this book is important discussion regarding the utilization of specific preoperative therapies to maximize surgical outcomes in patients with borderline resectable pancreatic cancer. Although some authors and centers utilize various preoperative modalities interchangeably, the author's personal preference has been for the use of extended induction systemic chemotherapy, followed by locoregional radiation treatment, prior to surgical resection in patients with anatomically borderline or locally advanced cancers. This allows patients to receive all the benefits of modern standard of care therapy prior to consideration of major resectional procedures, and maximizes probability of long-term survival by combining all effective available therapies in those patients most likely to benefit from aggressive operations.

Within this context, the concept of resectability continues to expand. Therefore, surgeons involved in the surgical care of patients with pancreatic cancer need to have significant experience in advanced techniques in order to render potentially life-extending surgical therapy. This chapter will focus on indications, techniques, and pitfalls of vascular resection in anatomically borderline resectable pancreatic cancer.

Venous Resection

An operation for pancreatic cancer is only of oncologic benefit if the following requisites are met: (1) the tumor can be resected with a negative margin—dependent on the extent of the local involvement of tumor, the complexity of the operation, and the experience and technical expertise of the surgeon; (2) no evidence or suspicion of metastatic disease exists—there is no survival benefit for surgery in such patients; and (3) the patient can tolerate the operation with limited and reversible perioperative complications and have a reasonably acceptable postoperative quality of life. In order to meet these requirements, the goals of an oncologically sound pancreatic cancer operation are specific. These include surgical extirpation of the primary tumor to negative margins, conduct of an appropriate regional lymphadenectomy for therapeutic and prognostic purposes, and minimization of perioperative complications that will allow receipt of adjuvant systemic therapy.

It has been well established that margin status after pancreatectomy for pancreatic cancer correlates with long-term survival and margin positive resections lead to worse overall survival [5, 20, 21]. Positive margin resections also correlate with local recurrences that can lead to significant symptoms and at times life-threatening complications if uncontrolled [22]. There is an inherent risk of a positive margin resection using a surgery-first approach, as supported by data from numerous pancreatic cancer surgery adjuvant trials [20, 23]. The actual survival benefit of surgery in the setting of a positive margin is essentially negated given the improved results of modern

non-operative therapies. A negative surgical margin resection is the only specific variable that can potentially be surgeon controlled and it is therefore justifiably considered a metric of both surgeon and institutional quality of pancreatectomy for pancreatic cancer [24, 25].

The margin most frequently found to be positive following pancreatectomy is the retroperitoneal (SMA, uncinate) margin for head/uncinate/neck tumors. Microscopic involvement of this and other margins is clearly underreported as there is significant discrepancy between pathological assessment and clinical outcome, and identification of tumor cells at the margin depends both on the adequacy of resection and the quality of histopathologic processing [26, 27]. Obtaining a negative margin can be accomplished by either initial wide resection or with reexcision [28].

As venous involvement by pancreatic cancer is a frequent occurrence, all surgeons undertaking pancreatic resection, specifically pancreaticoduodenectomy, should be capable of performing venous resection and reconstruction as this finding may be unexpected and the extent of disease can only be fully determined once committed to resection. In patients with anatomically borderline resectable pancreatic cancer a negative margin may well not be possible without resection of the porto-mesenteric veins. Regional pancreatectomy with en bloc venous resection was shown to be feasible years ago, but was associated with high rates of morbidity and mortality and poor long-term survival. This has historically limited enthusiasm for such procedures [29]. Furthermore, concurrent venous resections can result in increased operating time, higher blood loss, and greater transfusion requirements, and some studies have suggested potentially increased perioperative morbidity [30]. However, numerous institutional series have since established that synchronous venous resection during pancreatectomy for cancer is safe and allows a larger proportion of patients to potentially benefit from surgical therapy by enabling a negative margin resection [31–34]. This appears also true for patients undergoing venous resection with more anatomically advanced tumors [35].

The strongest data available for concurrent venous resection are from recent systematic reviews evaluating over 2000 patients undergoing concurrent venous resection compared to over 8000 patients with pancreatectomy alone that have revealed that surgical morbidity and mortality and overall survival rates are comparable to standard pancreatic resections [36, 37]. As contemporary data support the use of venous resection at the time of resection for pancreatic cancer, any such techniques that may lead to a margin negative resection should be given consideration [33]. Some authors have even suggested routine segmental venous resection during pancreaticoduodenectomy regardless of actual anatomic involvement with data suggesting a potential survival benefit of such routine venous resections, however such a policy—although intriguing—is not readily supported [38].

In general terms, venous resection during pancreatectomy can be divided into three major types dependent on the location of tumoral involvement of the portomesenteric venous system: (1) Portal vein (PV) above the confluence; (2) PV/Superior Mesenteric Vein (SMV) involving the confluence; and (3) the SMV below the confluence. Various further classifications have been described based on the type and/or location of resection and reconstruction [39]. To date, the type of venous resection performed has not been included routinely in the published analyses of postoperative morbidity and mortality, and as a result, a recent proposed venous resection classification system has been described in order to more accurately detail these procedures for future study analyses: Type 1: partial venous excision with direct closure (venorrhaphy) by suture closure; Type 2: partial venous excision using a patch; Type 3: segmental resection with primary venovenous anastomosis; and Type 4: segmental resection with interposed venous conduit and at least two anastomoses [40].

The limiting factor for resectability in the case of venous involvement is the extent and complexity of the venous resection/reconstruction. This complexity is dependent both upon the surgeon and local tumor anatomy. Several anatomic and physiologic principles need to be considered including preservation of hepatopetal flow to the liver from the bowel, and reestablishment of

venous outflow from the stomach and spleen, if necessary, to minimize the risk of postoperative sinistral hypertension.

In general terms, the limits of venous resection extend proximally to the origins of the right and left portal vein bifurcation of the main portal vein and distally to the first-order terminal ileal and jejunal branches of the SMV within the mesenteric root. Obtaining safe and adequate complete proximal and distal venous exposure and control prior to commitment to the resection is crucial when embarking on such operations in borderline or locally advanced cancers. Proximal portal vein resection and reconstruction is technically easier to perform, as the vessel diameter is large enough to create a sufficient anastomosis. However, very proximal portal venous involvement may also be associated with concurrent hepatic arterial involvement as discussed later in this chapter. In cases of distal tumor infiltration far below the portomesenteric venous confluence, the decreasing vascular diameter of the SMV can limit the technical success of a venous anastomosis. Sacrifice of one of the first-order terminal ileal or jejunal SMV branches can be performed as long as patency of one branch is maintained, however dissection and venous control deep in the mesenteric root may be difficult, particularly in obese individuals [41]. Furthermore, a distal anastomosis to one of these terminal branches is tenuous given the thin wall and fragility of these veins. The operative surgeon should therefore only commit to resection if success of such distal reconstructions has a high likelihood of technical success. Tumor infiltration of the confluence itself may be focal or extensive, and may extend posteriorly to involve the superior mesenteric artery (SMA). Furthermore confluence resections introduce concerns of gastric and splenic venous outflow that need to be considered that will be discussed later.

In cases of suspected need for venous resection, the author's approach is to first gain complete exposure and control of the portomesenteric venous structures, first distally then proximally, before committing to pancreatic resection. This is particularly germane in borderline and locally advanced tumors where assessment of technical resectability can sometimes only be accomplished intraoperatively. With tumors involving the infrapancreatic SMV, normal tissue planes can easily be distorted. Furthermore, significant desmoplastic changes, either from tumor infiltration or radiation, may exist. I have found the use of intraoperative ultrasound assists in the identification of vascular structures when this area is involved with significant inflammatory changes and thickened tissue to minimize venous injury during this dissection. The gastrocolic venous trunk and the middle colic vein, both of which lead to the anterior/lateral SMV, are identified early in the dissection. The gastrocolic trunk is ligated in continuity and the middle colic may be ligated as well if necessary. Control is obtained of the distal SMV. Further complete distal dissection of the primary first-order terminal ileal and jejunal SMV branches for distal venous control is then performed with in the root. If the inferior mesenteric vein (IMV) drains as a separate trunk into the lateral infrapancreatic SMV, it should also be controlled. If technically feasible, the peritoneum of the inferior border of the pancreatic neck and body lateral to the SMV is opened, dissection caudal to the pancreas is performed, and the splenic vein is identified and controlled. Hilar dissection ensues and control of the proximal portal vein is then performed. If the proximal portal vein is involved with tumor the right and left main trunks may need to be dissected initially proximally then the dissection proceeds distally after careful identification of possibly involved arterial structures. After the portal vein is controlled there is complete venous control and then dissection under the pancreatic neck can be performed safely. This approach of complete venous control, although time-consuming and tedious, is critical in the event of inadvertent venotomy and necessary repairs can then be performed under controlled conditions.

After pancreatic transection, formal assessment of the tumor/vessel interface can be made and the type and complexity of venous resection required can be specifically determined. Some surgeons attempt to tediously dissect as much of the specimen from the vein in order to minimize the complexity of the resection and reconstruc-

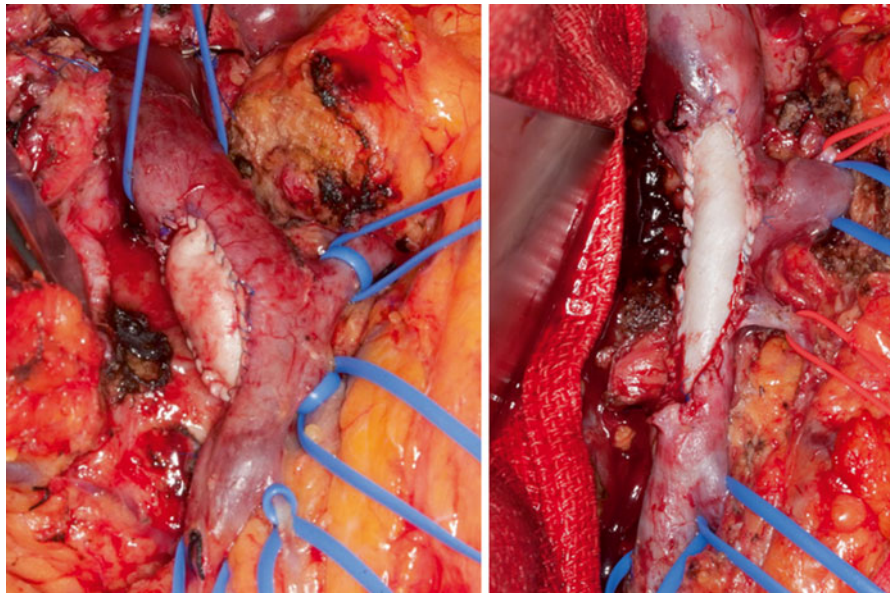

Fig. 13.1 Lateral tangential bovine patch venoplasty

tion. However, this can lead to inadvertent injury and/or a subsequent positive venous margin. In my practice any tissue that does not readily dissect off is considered at risk and removed en bloc with the specimen. This has resulted in a higher proportion of patients requiring more complex venous resections, however has significantly decreased intraoperative injury rates and subsequent venous margin positivity.

When tumor infiltration involves the right lateral circumference of the portomesenteric venous structures, a lateral tangential resection of the vein is possible. The tumor can be excised with a small en bloc segment of vein, and the vein can be repaired with either direct closure of the defect directly (if there is less than 25 % of the vein circumference involved) or with a patch venorrhaphy (using either autologous vein graft or bovine pericardial patch) without hemodynamically relevant stenosis (Fig. 13.1). We have found however that such lateral repairs or patches have led to subsequent significant stenosis with several patients requiring subsequent PV/SMV dilation and stenting due to developed mesenteric hypertension, gastrointestinal bleeding episodes, and ascites in long-term survivors. Thus we have moved towards formal segmental resection with either primary anastomosis or interposition grafts for most cases with any venous involvement. This practice also removes all "at risk" venous tissue and may potentially provide additional oncologic benefit.

If at all possible we prefer maximal attempts at full venous mobilization in order to construct a primary end-to-end anastomosis (Fig. 13.2). This can be performed with gaps up to 5 cm, and potentially more, depending on the specific patient anatomy. We perform full hepatic release and mobilization with right and left portal trunk dissection to gain additional length proximally and complete mobilization of the mesenteric root distally. The right colon should be completely mobilized inferiorly and medially from the retroperitoneal attachments of the anterior surface of the right kidney. This is continued dissecting the right and transverse mesocolon off the duodenum moving medially towards the groove between the uncinate of the pancreas and the mesenteric root. Our standard practice is to divide the splenic vein at the confluence not only to gain access to the SMA for the retroperitoneal dissection by allowing mobilization of the tumor and vein laterally,

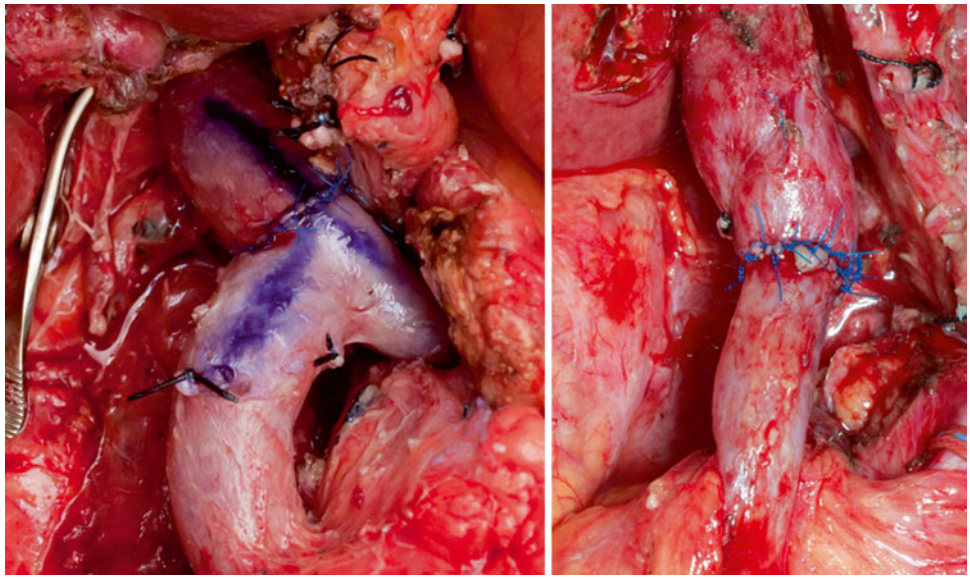

Fig. 13.2 Primary end-to-end venous anastomoses

but also for gaining additional centimeters of length for venous reconstruction. Such maneuvers allow significant added length and in most cases allow approximation of the distal and proximal resection vein margins without tension.

Reconstruction options for interposition grafts are variable and dependent on surgeon experience and comfort. Vein grafts such as left renal vein, internal jugular vein, saphenous vein, and deep femoral vein have all been described and the choice is surgeon- and experience-dependent (Fig. 13.3). We would caution the routine use of synthetic grafts, particularly in those patients predicted to have intermediate to high-risk postoperative pancreatic fistula, due to the life-threatening potential for post-pancreatectomy hemorrhage and/or difficult-to-treat long-lasting graft infection [42]. As pancreatectomy has a high risk of abdominal infection the use of synthetic venous prostheses might increase this complication [43]. One of the long-term risks of mesenteric venous reconstruction is subsequent thrombosis and occlusion with resulting complications and the use of synthetic grafts is a described risk factor for postoperative thrombosis [44].

We have recently increased the use of custom-fashioned bovine pericardial tube grafts created over a 28–32 Fr chest tube with an endovascular stapler to create tube grafts of various lengths (Fig. 13.4). These grafts are not only resistant to infection but this technique allows individual case tapering of the graft to the appropriate proximal and distal PV/SMV diameters. We have significant experience with such customized grafts with no significant detriment in patency or complications and this avoids harvest of other vascular conduits or use of synthetics for longer reconstructions. We orient the tube graft with the staple line either at the 12 or 6 o'clock position which allows the tube graft to assume a near perfect circular dimension once the viscera resumes normal position overlying the reconstruction. This provides ideal flow dynamics without the elliptical compression that might occur if oriented otherwise. In all cases of interposition grafts, care must be taken to avoid excess length and possible kinking of the graft or vein above and below that can lead to postoperative thrombosis and may require early operative revision.

Although the bulk of the literature and practice of venous resection in pancreatectomy is during pancreaticoduodenectomy, venous procedures may also be required during distal or total pancreatectomy. Tumors in the left neck or body of

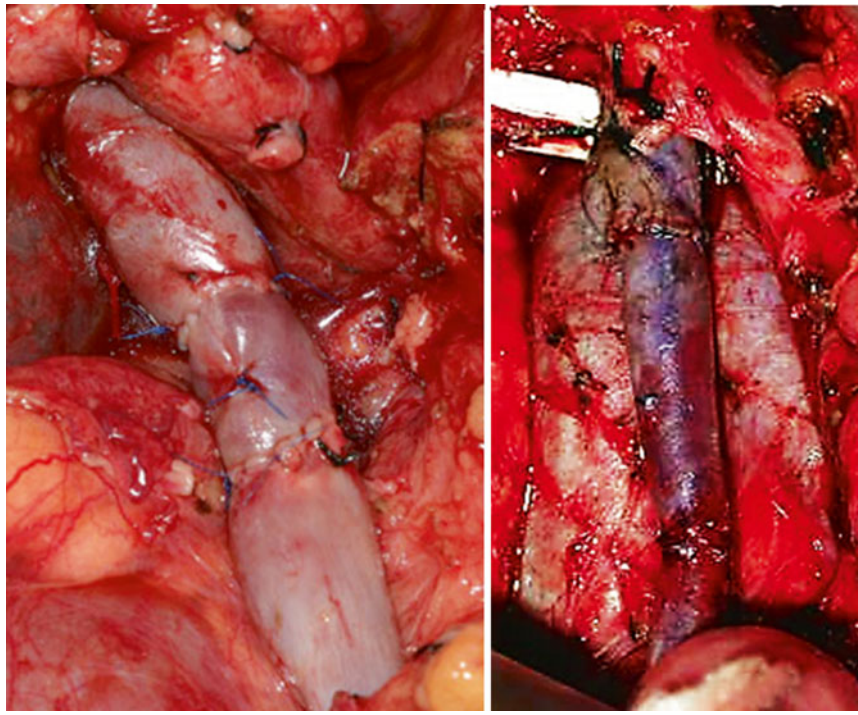

Fig. 13.3 Autologous vein interposition grafts (left renal vein and internal jugular conduits)

the pancreas can undergo subtotal extended distal pancreatic resection with the limits of proximal pancreatic resection determined at the level of the gastroduodenal artery (GDA), a natural anatomic landmark. This allows preservation of the duodenum and head of the pancreas. Care must be taken however as any resections beyond the GDA carry risk of inadvertent bile duct injury. In such extended resections with tumors arising in the pancreatic neck/body, often the splenic vein is occluded up to or involves the confluence and may extend into the PV/SMV. Such cases are reconstructed with either lateral patch grafting or formal segmental resection and anastomoses, either primarily or with conduit as described earlier.

In my practice I perform temporary SMA inflow occlusion during the venous reconstruction to prevent bowel wall congestion and edema that will hinder subsequent anastomoses. Soft plastic atraumatic bulldogs clamps are recommended to avoid intimal injury. Rummel tourniquet occlusion has also led to cases of arterial injury and is generally avoided. If the venous reconstruction can be performed in a rapid fashion, temporary SMA occlusion is optional. We prefer use of systemic heparin at the time of venous resection without reversal and continue postoperative heparin prophylaxis for 30 days. Finally we highly advocate the use of duplex ultrasound after every reconstruction to confirm patency and normal flow dynamics.

Sinistral Hypertension and Shunting Procedures

One of the most often unappreciated aspects of venous resection in pancreatectomy is the maintenance or re-establishment of gastrosplenic venous outflow. If the confluence including the splenic vein requires resection or is ligated for additional venous length and/or due to need for direct access to the SMA for the retroperitoneal dissection, postoperative acute sinistral hypertension may develop if adequate gastrosplenic

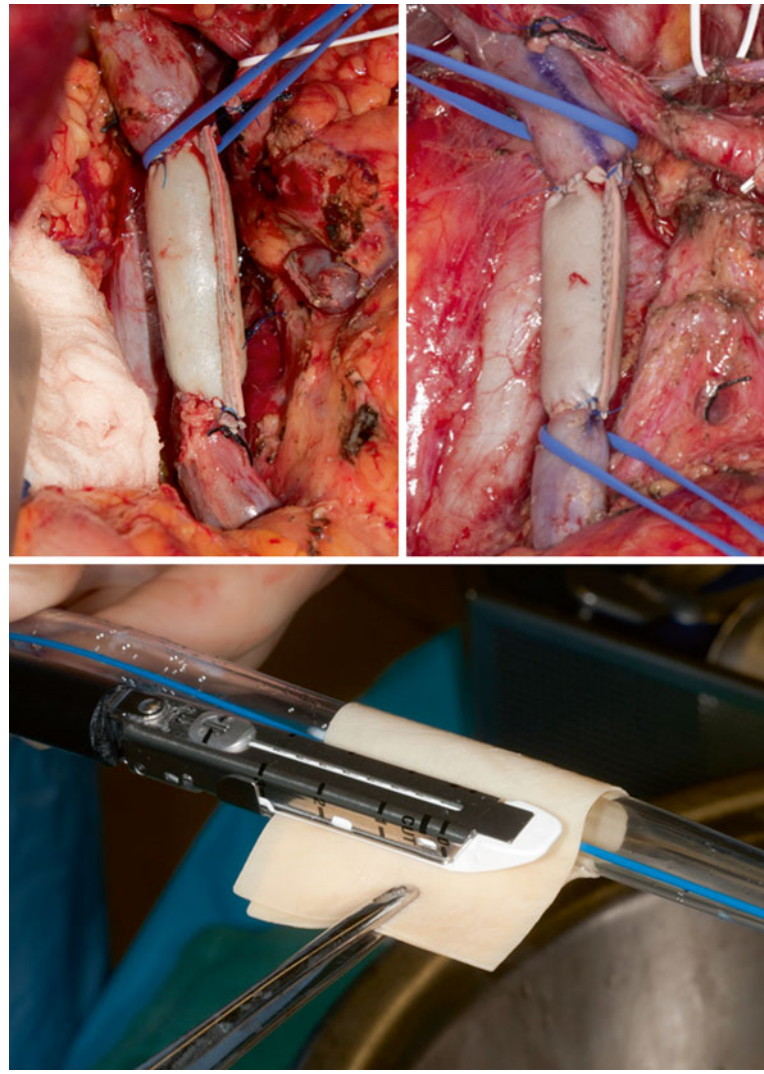

Fig. 13.4 Custom-fashioned bovine pericardial tube interposition grafts

retrograde outflow collaterals (IMV, coronary vein, gastroepiploic vein via gastrocolic trunk) are either anatomically unavailable or have been ligated as a result of the resection. In such circumstances our practice is to construct a distal splenorenal shunt (DSRS) to avoid the possibility of abrupt segmental left-sided venous hypertension that can result in splenomegaly with resultant acute hypersplenism, hypertensive gastropathy, varices, and subsequent postoperative hemorrhage that has occurred in several patients.

Recent reports have provided a proof of concept for the safety and efficacy of such venous decompressive techniques [41, 45, 46]. In the majority of cases the IMV terminates proximally into the inferior border of the splenic vein at its midpoint or near the splenoportal angle. The presence of this natural anatomic outflow pathway provides sufficient venous drainage of the spleen and gastric remnant and should be safely preserved and left in situ to provide retrograde sinistral outflow after splenic vein division. However, in up to one-third of patients, the IMV drains into the SMV as a separate trunk. Acute postoperative sinistral hypertension can thus develop after splenic vein division or resection.

For oncological necessity, particularly with microscopically invasive pancreatic adenocarcinoma, wide vascular resection of the portal venous confluence including the IMV is often necessary. Furthermore, ligation of the left gastric vein (coronary vein) performed during lymphadenectomy may also limit gastric remnant venous drainage. In such cases, splenic vein shunting can be particularly useful and may mitigate the risks of sinistral hypertension. The need for splenic venous shunting can be predicted preoperatively on coronal imaging based on the anatomical variant of IMV insertion, as well as intraoperatively estimated after splenic vein division by identification of dilated gastric veins, a dusky, boggy appearance to the stomach, and turgor in the divided splenic vein itself.

Construction of the anastomosis technically requires adequate visualization of the left renal vein, which is identified underneath and to the left of the SMA. The renal vein can be further mobilized, if additional length is needed, by ligation of the left gonadal and/or adrenal vein. We do not advocate reimplantation of the splenic vein to the newly created portomesenteric venous reconstruction as this may result in flow dynamic changes as a result of kinking of the anastomosis, and subsequent thrombosis can propagate from the splenic vein into the newly reconstructed PV/SMV and result in mesenteric outflow obstruction with resultant bowel congestion and possible venous ischemia and liver dysfunction in addition to gastrosplenic hypertension.

In patients undergoing total pancreatectomy, in whom the short gastric venous collaterals are typically divided as part of splenectomy, venous resection may lead to severe venous congestion of the remaining stomach that may require extended gastric resection to avoid ischemic complications. In these cases careful preservation of the coronary vein may allow adequate gastric venous drainage without need for formal gastric resection.

In patients with preoperative SMV/PV occlusion secondary to tumor infiltration or thrombosis, numerous high-pressure, thin-walled venous collaterals develop around the pancreatic head and neck in order to decompress the mesenteric venous system. Pancreatic resection and concurrent venous reconstruction in these cases is considerably high risk as they are often complicated by significant venous hemorrhage. Furthermore, the ligation of such collaterals during the course of the operation further contributes to mesenteric hypertension and bowel congestion. In an effort to minimize intraoperative bleeding and simultaneously allow adequate hepatopetal outflow, the use of a temporary mesocaval shunt (MCS) can be utilized. This procedure is performed early on in the operation before the resectional procedure and portal dissection to avoid injury to these high-pressure, high-flow collaterals. Our preference is to use autologous internal jugular vein as the interposition graft as it is pliable enough and of adequate length to initially bring towards to the anterior surface of the inferior vena cava for temporary intraoperative mesenteric outflow shunting during the resection portion of the case. Once the specimen is removed it is a straightforward procedure to then subsequently transpose this graft to the proximal portal vein for completion of the portomesenteric reconstruction following resection. Temporary PTFE grafts can also be utilized in this setting if additional length is needed for shunting and after resection can be removed with either primary end-to-end venous anastomosis or with interposition grafting. The need for construction of a concomitant DSRS during mesocaval shunting is best anticipated before splenic vein ligation, when venous pressure is lowest, in order to dissect an adequate length of splenic vein from the undersurface of the remnant pancreas to reach the left renal vein.

Arterial Resection

Arterial resection for pancreatic cancer has historically been considered contraindicated due to its associated operative morbidity, high margin positive resection rate, and dubious survival advantage [29]. Although complex arterial resections have been performed in selected patients, it is still regarded as an extraordinary approach as arterial infiltration is typically a surrogate of a biologically aggressive tumor with high likelihood

of occult disseminated disease rather than just a function of tumor location. Although anatomically borderline resectable criteria include isolated common hepatic artery involvement and partial SMA abutment, an initial resection, even if it can be technically performed, is currently not recommended in the absence of preoperative treatment and appropriate patient selection. Even greater caution is advised in proceeding with arterial resection in those tumors classified as anatomically locally advanced/unresectable.

However, this dogma has now been challenged with the introduction of effective modern therapeutics: the current anatomic arterial classification of locally advanced tumors does not categorically imply unresectable disease per se. As surgical resection remains the only hope for cure, more aggressive surgical approaches may be advocated to increase resection rates and institutions have released data on their experience with pancreatectomy and simultaneous arterial resections. Data from several small series of arterial en bloc resections suggest that such aggressive operations can result in relatively comparable overall survival to standard resections and thus can be justified in highly selected patients [47, 48]. The best available data comes from a recent meta-analysis of 26 studies of 366 and 2243 patients who underwent pancreatectomy with and without arterial resection. The cumulative data reveal that arterial resections are associated with longer operative times, increased intraoperative blood loss, prolonged length of stay, increased morbidity (median 53.6 %) (with a significant proportion of patients [17 %] suffering from bleeding, thrombotic, or ischemic complications), and increased perioperative mortality (median 11.8 %) when compared to those patients without arterial resections. Overall survival rates were similarly worse among patients who underwent arterial resection. However, these data did suggest improved long-term survival compared to patients with locally advanced disease who did not undergo resection [49].

With the use of improved systemic and locoregional therapies, aggressive operations with arterial resection may offer substantial benefit after extensive preoperative treatment, albeit with significant perioperative risk. Our own large experience with arterial resections in patients with a locally dominant phenotype has confirmed this conclusion. The administration preoperative therapy prior to consideration of arterial resection has been widely accepted [33]. All patients with any degree of arterial involvement should be considered for neoadjuvant therapy which in our opinion should invariably include: induction systemic chemotherapy—treatment of occult metastases, potential downstaging of primary tumor; and locoregional irradiation—treatment of primary tumor and surrounding at risk structures for local tumor control and to maximize possibility of a potential margin negative resection. Only after such standardized treatment should consideration of surgical resection be entertained as results of nonoperative therapy using this sequencing suggests nearly equivalent outcomes compared to surgery alone for such advanced cases [7]. As a disclaimer the arterial procedures that will be described are currently not recommended and should only be considered in highly selected patients at experienced and specialized centers ideally under protocol-based or clinical trials settings.

The arterial structures that are at risk for locoregional tumor involvement include the celiac, hepatic, and superior mesenteric arteries. In addition variant hepatic arterial anatomy places such vessels at risk, most commonly a replaced right hepatic artery [33]. Celiac stenosis caused by atherosclerotic disease or median arcuate ligament compression is another potential indication for arterial procedures. Types of arterial procedures include primary repair or angioplasty, resection and/or ligation alone without reconstruction, resection with primary anastomosis, and resection with interposition grafting, and complex revascularization. Simply stated, the more extensive the arterial involvement the more technically complex the required procedures are in order to render a negative margin resection and the more ensuing attendant morbidity and mortality. Therefore, patient selection for such procedures is of paramount importance and just as critical as technical expertise taking into consideration patient age and expected life-expectancy,

grade of comorbidities, performance status, and anticipated quality of life. In our experience, the ideal patients for such aggressive operations are relatively young, fit, sophisticated to understand the risks and potential for limited oncologic benefit, and have undergone extensive preoperative therapy with some objective measure of efficacy. Such exceptional procedures are definitively not widely recommended but may have a role in highly experienced and specialized centers.

Critical in cases requiring arterial resection is the establishment and maintenance of adequate hepatic, gastric, and visceral perfusion. The potential anatomic limits of arterial resection extend distally from the right and left hepatic artery bifurcation of the proper hepatic artery to the celiac axis, its branches, and the proximal SMA. Tumor infiltration into the porta hepatis beyond 1–2 cm above the proximal sectoral hepatic artery bifurcation implies unresectability as these vessels are often small in caliber and resulting anastomotic failure will have significant hepatic and biliary consequences. As the biliary system relies on this arterial inflow, failure to accomplish this either technically or due to postoperative occlusion/thrombosis can lead to anastomotic breakdown and leak, stricture, or intrahepatic abscesses that can be extremely difficult to manage.

Tumors in the pancreatic head may extend medially along the common hepatic artery towards the celiac. Hepatic artery resection up to the proximal common hepatic artery root is possible with graft conduits. Simultaneous resections of celiac axis and hepatic arteries with complex revascularization have been performed with oncologic success. However, such cases also may also require total pancreatectomy and gastrectomy. The extent of arterial involvement that needs to be resected determines the extent of pancreatic resection and other organs required to accomplish this. Such multivisceral resections are required due to ischemic consequences of these procedures and may further increase the resultant risks [50, 51].

En bloc celiac artery resections are almost exclusively performed as part of distal pancreatic resections for anatomically locally advanced body tumors and have been shown to be feasible while allowing a reasonably acceptable margin negative resection rate and the potential to achieve significant local tumor control in selected patients [52, 53]. Due to the extensive arterial collateral circulation via pancreaticoduodenal arcades from the SMA through the GDA, hepatic and gastric perfusion can be maintained in most cases as long the tumor spares the proper hepatic artery distal to the GDA (Fig. 13.5). These cases

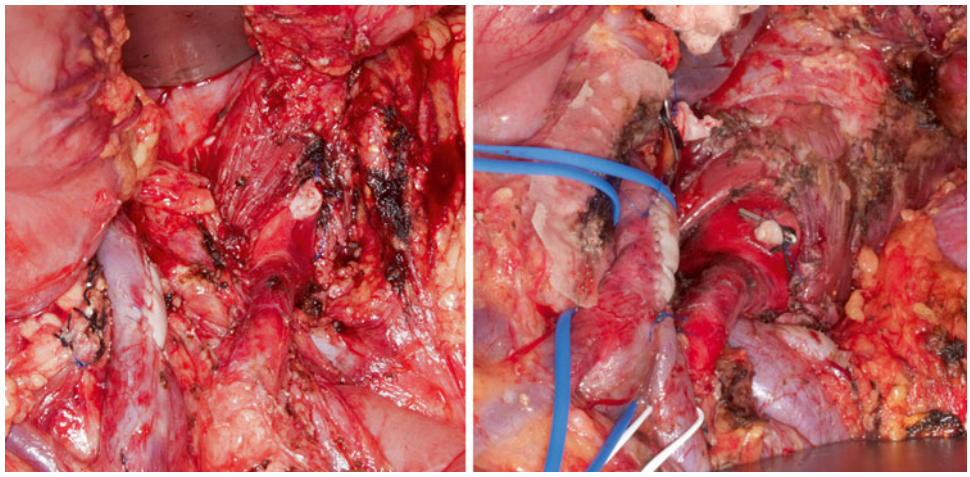

Fig. 13.5 R0 extended distal pancreatectomies with en bloc resections of tumor involved celiac arteries without arterial revascularization and concomitant bovine pericardial patch venoplasties. Patients underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

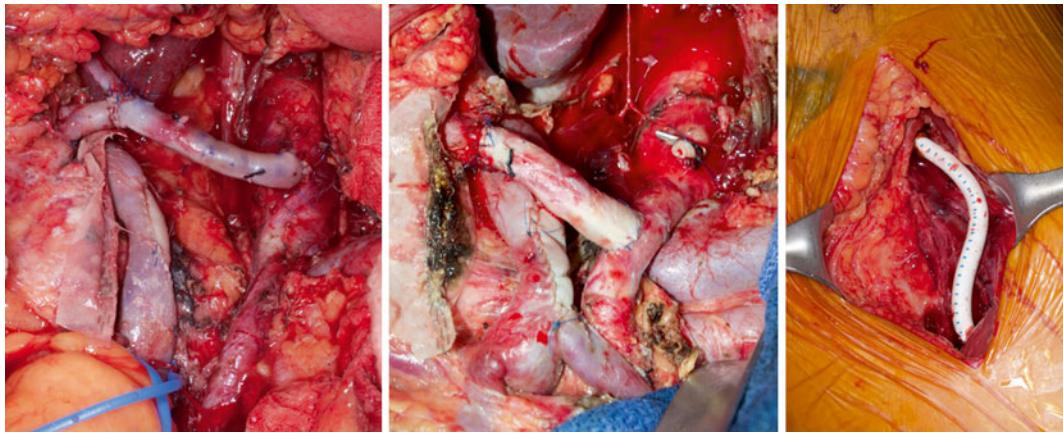

Fig. 13.6 R0 extended distal pancreatectomies with en bloc resections of tumor involved celiac arteries with arterial revascularization via SFA jump grafts from celiac stump or lateral SMA and concomitant bovine pericardial patch venoplasties. SFA harvest site is reconstructed with PTFE graft in lower extremity. Patients received extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

commonly require some form of venous resection due to venous infiltration.

If hepatic or gastric perfusion is determined to be insufficient following temporary occlusion of the common hepatic artery or if the GDA and proper hepatic artery need to be resected for more extensive tumors, then conduit bypass grafting needs to be performed to avoid ischemic complications. This can be performed with a variety of conduits. We prefer the superficial femoral artery (SFA), which is of adequate length and diameter and is also thick enough to resist complications from postoperative pancreatic fistula. SFA is harvested from the lower extremity and replaced with a PTFE graft. SFA jump grafts to the distal hepatic artery can be anastomosed to the stump of the celiac artery, the supraceliac aorta, or the lateral SMA (Fig. 13.6). Intraoperative perfusion of the stomach should be carefully inspected as the left gastric and short gastric vessels via the splenic artery are resected en bloc with such resections. More complex advanced resections include extended distal pancreatectomy with en bloc celiac and SMA resections and revascularization for body tumors (Fig. 13.7). The higher incidence of POPF in patients undergoing distal pancreatic resection can severely comprise celiac procedures; thus all methods to decrease the incidence and severity of fistula should be employed.

For those cases where there is potential for SMA involvement, approaches to delineating resectability prior to resectional commitment include various artery-first strategies including left and right-sided dissections and infra- and supracolic approaches. After significant preoperative therapy including radiation, the residual soft tissue involving the SMA has been found in several cases to contain only fibros is and treated nonviable tumor on final pathologic processing; thus an argument for a planned R1 resection may exist in certain cases. The problem with this approach is that such a dissection is significantly difficult and may result in formal arterial injury thus not recommended unless performed with experienced hands capable of performing a repair if necessary. In some cases, there may exist extension of tumor infiltration deep into the mesenteric root involving multiple jejunal inflow vessels (Fig. 13.8). Furthermore it is exceedingly rare to not simultaneously require extensive venous confluence resection that often is the limiting anatomical factor to resection. Despite our group's highly aggressive approach to tumors with extensive vascular involvement, simultaneous segmental PV/SMV and SMA resection carries with it prohibitive risk as complications with either vessel reconstruction can lead to fatal consequences and is not currently pursued.

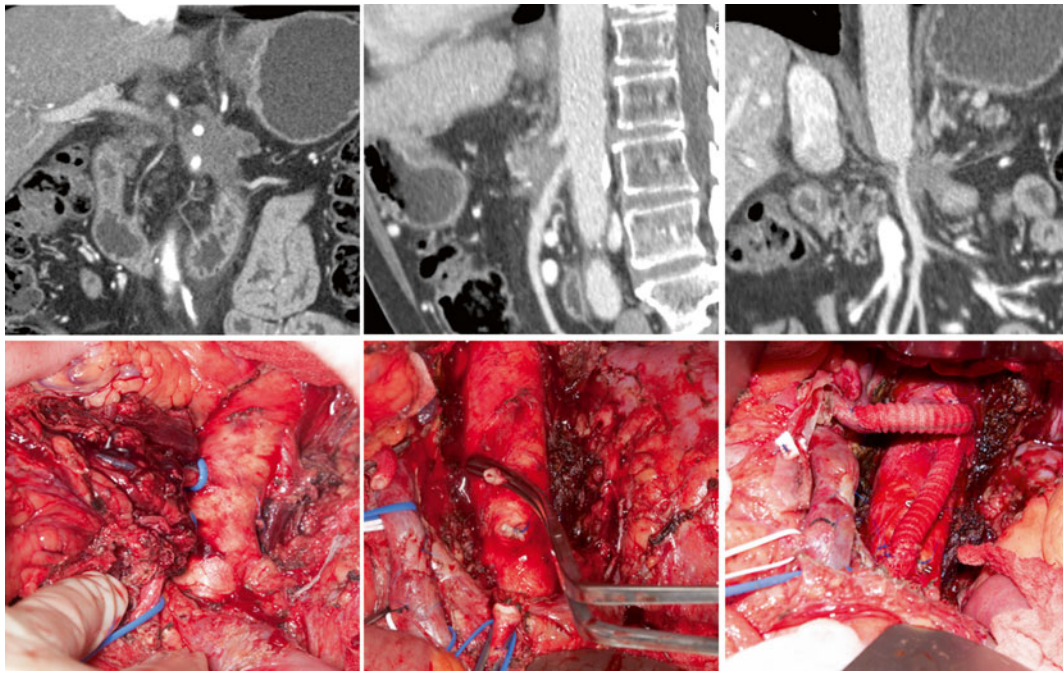

Fig. 13.7 R0 extended distal pancreatectomy with en bloc resection of tumor involved celiac and SMA with arterial revascularization via bifurcated rifampin-soaked Dacron graft from supraceliac aorta to distal HA and SMA and concomitant bovine pericardial patch veno-plasty. Patient underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection without radiographic response; however, no viable tumor in resected specimen. Currently NED 29 months from diagnosis

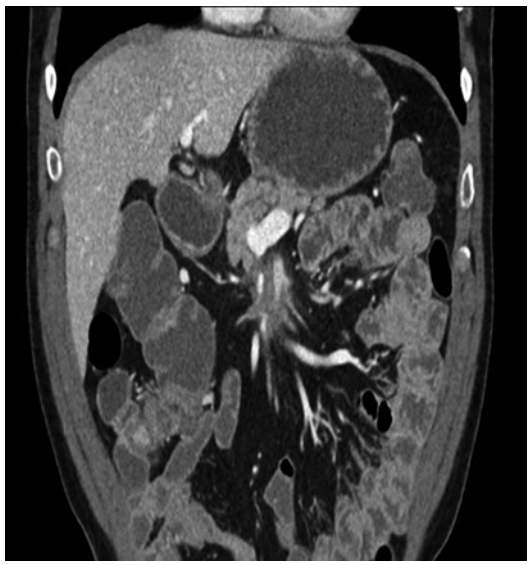

Fig. 13.8 Radiographic example of truly unresectable SMA/SMV tumor infiltration into mesenteric root

Our current recent practice for head tumors requiring simultaneous portovenous and hepatic arterial resection is to perform total pancreatectomy with en bloc vascular resection. This allows the use of the splenic artery as a conduit arterial graft that can either be harvested from the uninvolved pancreas as a jump graft or kept in situ and rotated to the right as a transposed neohepatic artery (Figs. 13.9, 13.10, 13.11, and 13.12). This approach although does result in permanent pancreatic insufficiency and diabetes but completely eliminates the risk of pancreatic fistula that in our experience is the single factor responsible for major morbidity and mortality in arterial resection cases. Bleeding and thrombotic complications after such dual vessel complex procedures can be life-threatening and are no longer amenable to traditional interventional procedures as the anatomy has been surgically altered.

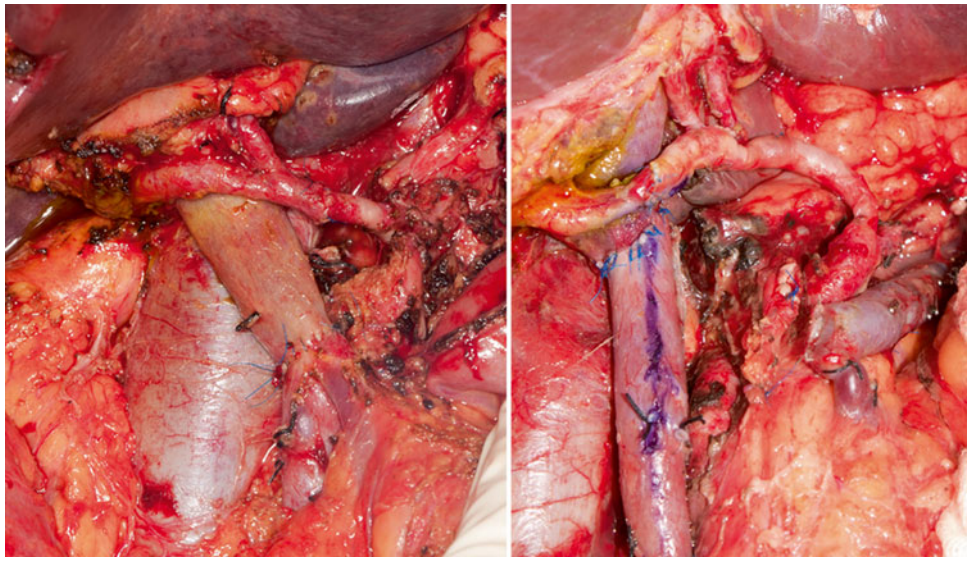

Fig. 13.9 R0 total pancreatectomies with en bloc resection of tumor involved hepatic arteries with revascularizations via splenic artery transpositions to create "neohepatic" arteries and concomitant segmental PV/SMV resection with primary venous anastomoses. Patients underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

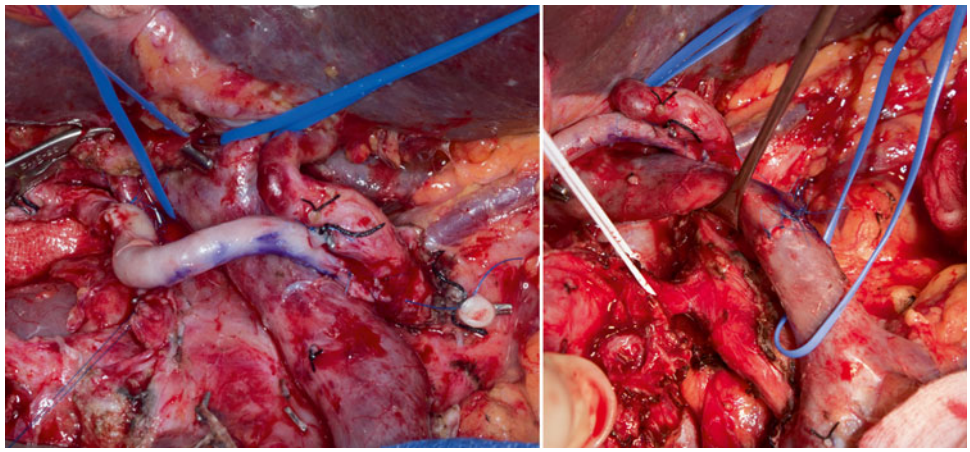

Fig. 13.10 R0 total pancreatectomy with en bloc resection of tumor involved replaced right hepatic artery with revascularization via splenic artery jump graft from ligated GDA proximal to distal right hepatic artery and concomitant segmental PV/SMV resection with primary venous anastomosis. Patient underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

Head tumors that involve a replaced right hepatic artery arising from the lateral proximal SMA can also be resected and reconstructed. Although some have suggested simple ligation, biliary consequences of arterial ischemia will lead to significant complications. Primary anastomoses can sometimes be performed if the involvement is focal. Otherwise, jump grafts from the proper or common hepatic artery or even the ligated GDA stump to the uninvolved proximal right hepatic artery may allow establishment of hepatic arterial inflow (Figs. 13.10

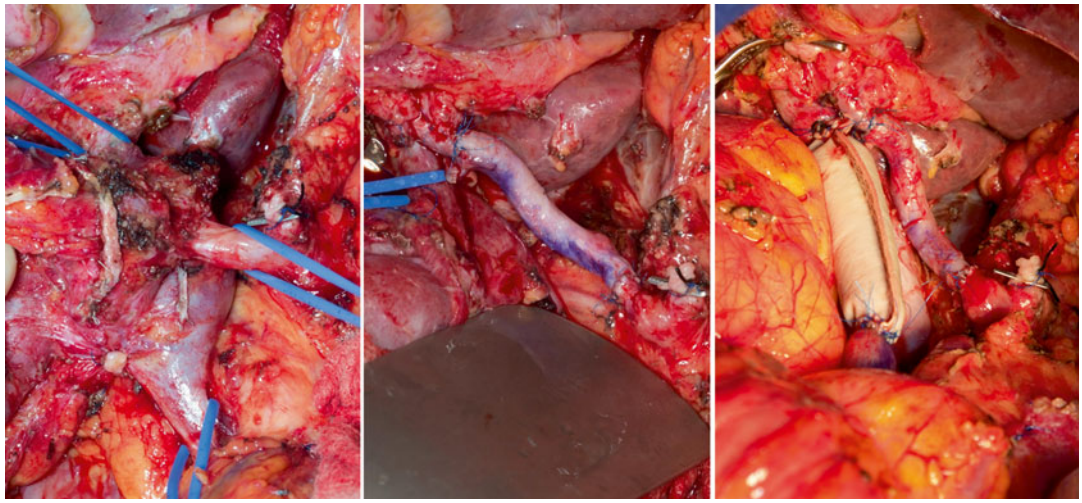

Fig. 13.11 R0 total pancreatectomy with en bloc resection of tumor involved proper and common hepatic artery with revascularization via splenic artery jump graft from CHA stump to right and left hepatic artery bifurcation and concomitant segmental PV/SMV resection with custom-fashioned bovine pericardial tube graft. This patient was previously explored elsewhere and deemed unresectable intraoperatively. Patient underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

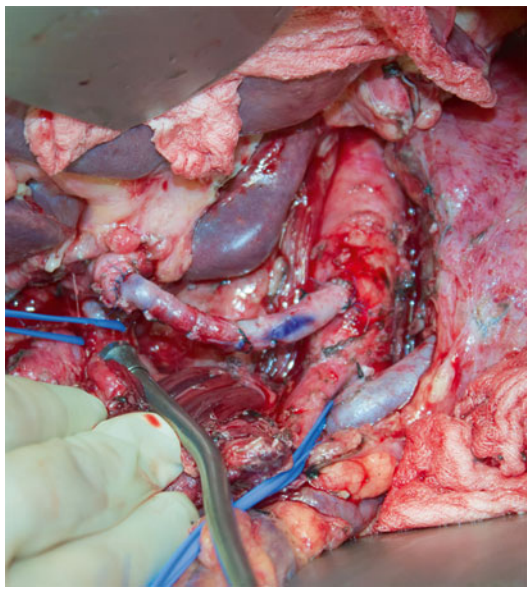

Fig. 13.12 R0 total pancreatectomy with en bloc resection of tumor involved proper hepatic, common hepatic artery, and celiac axis with revascularization via splenic artery jump graft from celiac stump to distal proper hepatic artery. Multivisceral resection requiring total gastrectomy. Patient underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

and 13.13). The proximal extent of the replaced hepatic artery as it arises from the lateral SMA should be carefully ligated at the time of en bloc specimen removal to prevent subsequent pseudoaneurysm formation.

All patients who undergo arterial resection should receive systemic heparin anticoagulation and the reconstruction should be performed early in the case, prior to specimen resection and/or concurrent venous resection/reconstruction. With simultaneous en bloc celiac and/or hepatic artery and portovenous reconstruction, hepatic ischemia time should be minimized. Postoperative liver function tests should be followed until the trend has normalized and any persistent elevations or increases should be thoroughly investigated to assess for graft problems. Our practice is to start ASA at the end of the operation and this is continued along with prophylactic heparin administration postoperatively. We obtain intraoperative formal duplex imaging and postoperative CT angiography if renal function is preserved to confirm technical success as this policy has identified several cases that required early intervention to prevent graft failure. As surgery-related major

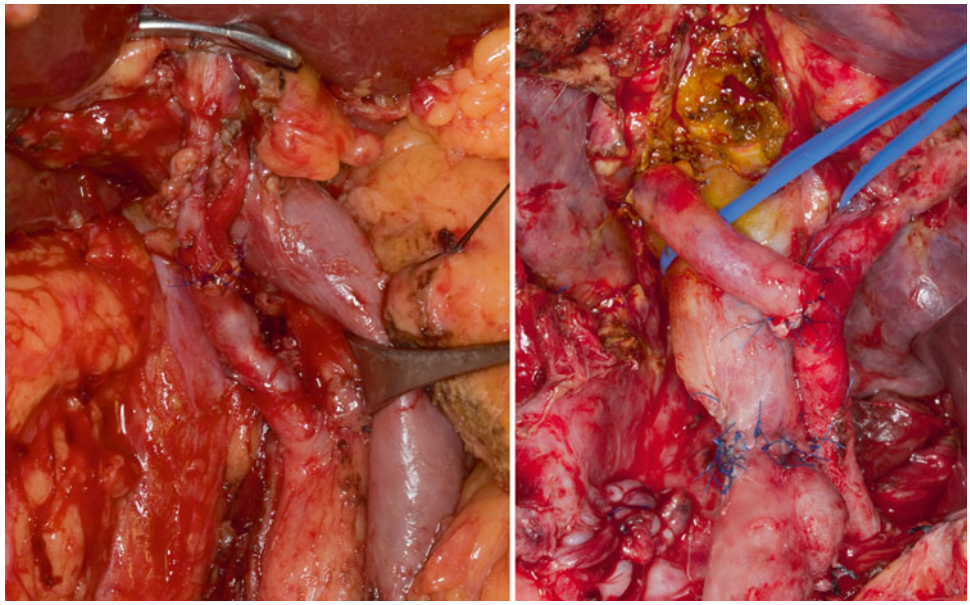

Fig. 13.13 R0 pancreaticoduodenectomies with en bloc resections of tumor involved replaced right hepatic arteries with revascularizations via primary anastomosis and saphenous vein jump graft from left hepatic artery to distal right hepatic artery and concomitant segmental PV/SMV resection with primary venous anastomosis in one case. Patients underwent extensive preoperative induction systemic chemotherapy and consolidative chemoradiation prior to resection

morbidity diminishes the oncologic efficacy of a margin negative pancreatectomy, patients undergoing such advanced procedures should be cautiously observed with a sense of urgency for any potential complication [54].

Preoperative Therapy

Approximately one-third of initially anatomically staged unresectable tumors are expected to convert to resectable tumors following neoadjuvant therapy with favorable outcomes thus should be included in neoadjuvant protocols and subsequently reevaluated for resection [55]. High-quality cross-sectional imaging can highly predict vascular involvement and need for vascular resection and various grading systems have been established with utilization of standardized imaging reporting templates; however, there is no consensus on grading response to therapy in pancreatic cancer [3, 56–60]. In contrast to other centers we do not rely solely on such radiologic downstaging after preoperative therapy to consider patients for arterial resection. Imaging poorly correlates with subsequent pathologic response after neoadjuvant therapy so in the absence of metastatic disease, resection should be considered if technically feasible [61, 62]. The author's significant personal experience of over 150 resections of borderline/locally advanced cancers after protocol-based neoadjuvant therapy supports the failure of traditional radiographic measures of response in these cases and other methods such as diffusion-weighted MR sequences and newer functional imaging (PET/CT/MR) scanners. Our current criteria for proceeding with operative intervention is foremost the absence of metastatic disease and other surrogates of response such as nutritional stabilization, cessation of preoperative pain symptoms, improved physical performance, and a biochemical tumor marker (CA19-9) response. Furthermore the planned resectional procedure should include resection of all potential residual disease with planned complex vascular and

gastrointestinal resection and reconstruction as indicated. Often the persistent low-density residual tumor infiltration along critical vessels is found to have significant treatment effect and little viable tumor thus the potential for a true and oncologically beneficial negative margin can be achieved with advanced techniques in properly treated and selected patients [63, 64].

The author's standard protocol for all patients with borderline/locally advanced tumors is initial patient-risk stratification assessing anatomic, biological, and conditional characteristics. Patients with any borderline features or anatomically locally advanced tumors are considered for neoadjuvant therapy and this has invariably begun with extended induction systemic chemotherapy followed by chemoradiation with drug choices dependent on patient-specific factors [65, 66]. Caution should be considered with extended cycles of modern chemotherapeutics as this increases treatment-related toxicity as well as increase the risk of chemo-associated liver disease. We have found that patients that complete this admittedly difficult preoperative regimen, regardless of initial locoregional tumor extent, can expect significant oncologic benefit. Furthermore in those patients who are initially deemed unresectable at previous exploration, salvage pancreatectomy after such a multimodal strategy is feasible and can lead to with favorable long-term outcomes in the majority of cases [67].

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Artery-First Approaches to Pancreaticoduodenectomy

14

Kyoichi Takaori and Shinji Uemoto

Introduction

Pancreaticoduodenectomy (PD), also known as the Whipple procedure, has been practiced for nearly a century [1]. Historically, the primary challenge of this operation has been overcoming the morbidity associated with the tenuous pancreatico-enteral anastomosis required to reconstruct the gastrointestinal tract following tumor resection. However, the refinement of perioperative techniques over the years has reduced the morbidity associated with this portion of the operation to acceptable levels. Now, surgeons face a more difficult challenge: achieving negative surgical margins in the setting of borderline and locally advanced pancreatic cancer. In this article, we present our techniques of artery-first PD as a means to achieve a high rate of margin-negative resection under these circumstances, and we also present a review of the literature on this technique.

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History of Artery-First PD

In 1993, Nakao and Takagi first proposed the concept of "Isolated pancreatectomy" [2]. Their idea was to isolate the blood flow to tumors in the pancreatic head by ligating the feeding arteries and bypassing portal venous flow using a catheter. They described a technique of a "mesenteric approach," in which the superior mesenteric vein (SMV) and superior mesenteric artery (SMA) were approached from the mesentery of the jejunum at the base of the transverse mesocolon. This technique allowed early division of the inferior pancreaticoduodenal artery (IPDA) and meticulous dissection along the SMA. Nakao's paper of isolated pancreatectomy appears to represent the first description of an "artery-first" approach to PD, though they did not use this term.

Weitz and his colleagues first proposed the term "artery-first approach" in the English literature in 2010 [3]. Since then, many surgeons have described different methods of artery-first approaches to PD. In our review of the literature, we identified six primary methods for an artery-first approach to PD, or "artery-first PD" (Fig. 14.1) [4]. However, a well-accepted, uniform definition of "artery-first PD" has not been established to date.

Based on the six primary methods of artery-first approaches to PD (Fig. 14.1), many other variants have been described; for example, we

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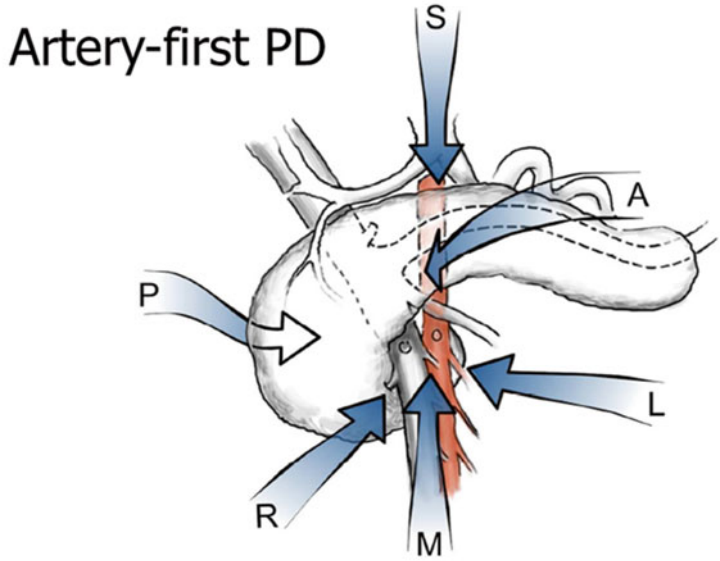

Figure 7: Demonstrating the 6 approaches to the SMA. S- superior approach, P- posterior approach, R- right/medial uncinate approach, M- mesenteric approach, L- left posterior approach, A- anterior approach.

Fig. 14.1 Diagram showing the six approaches to the superior mesenteric artery. *S* superior approach, *A* anterior approach, *P* posterior approach, *L* left posterior approach, *R* right/medial uncinate approach, *M* mesenteric approach. This figure was reproduced from [4] with a permission of the publisher

have adopted an artery-first approach to distal pancreatectomy with celiac artery resection [5]. Herein we define "artery-first pancreatic resection" as any pancreatic operation in which any technique is used to ligate the feeding arteries before the division of the pancreas with the intent of reducing blood loss and of achieving a more oncologically complete resection.

Advantages of Artery-First PD

Although the majority of surgeons initiate the dissection in a standard PD with a Kocher maneuver, an increasing number of surgeons are performing an artery-first PD. Putative merits of this general approach include (1) reduction of intraoperative blood loss, (2) early determination of arterial involvement by tumor, (3) clearance of surgical margins along the arteries, and (4) ultimately, a more oncologically complete resection.

In a case-matched study comparing artery-first PD using a posterior approach ($n=21$) versus standard PD ($n=21$), there was a significantly lower mean blood loss ($P=0.0314$) and a shorter operative time ($P=0.0002$) associated with artery-first PD. There were no significant differences identified in rates of early morbidity and mortality, length of hospitalization, overall survival, and survival according to tumor type [6]. In another series reported by Kurosaki and his colleagues, there were no significant differences in operating time, blood loss, hospital stay, or overall morbidity between the group of patients who underwent artery-first PD by the left posterior approach ($n=40$) and that of patients who underwent standard PD ($n=35$). However, artery-first PD was associated with fewer recurrences ($P=0.006$) and improved 1- and 3-year survival rates ($P=0.004$) compared to standard PD [7]. Though additional retrospective studies exist in which artery-first PD and standard PD are compared, their results are inconsistent and

no conclusions can generally be drawn from them. Controlled randomized trials are needed to validate the potential advantages of artery-first PD.

Role of Artery-First PD

Artery-first PD has been practiced for two decades by enthusiastic pancreatic surgeons and it is routinely used in many specialized institutions in Japan [4]. In contrast, artery-first PD has been less popular in Western countries, possibly due to difficulty in identification and dissection of arteries in obese patients. Worldwide, there is an increasing role for artery-first PD given the increasing role for surgical resection in the setting of borderline resectable pancreatic cancer [8]. Indeed, consensus exists that operative exploration and resection may be indicated, in high-volume centers with surgical and multidisciplinary expertise, in the case of involvement of SMV and/or portal vein or limited involvement of the SMA, but not in that of arterial encasement [9]. Therefore, it has become necessary to assess for the presence or absence of arterial encasement at an early stage of pancreatectomy. The artery-first PD is an ideal approach to this clinical problem.

The artery-first PD is also appropriate following administration of chemotherapy and/or chemoradiation [10]. Indeed, pancreatic surgeons are asked to resect ever-increasing numbers of patients with borderline resectable and locally advanced pancreatic cancer who have received prior induction therapy. It is not possible to predict pathologic involvement of the SMA after neoadjuvant therapy by imaging alone because fibrotic tissue may often remain after treatment even in the setting of a significant pathologic response. Upon surgical exploration, surgeons must dissect around the major arteries such as the SMA and GDA and decide whether or not to resect before the "point of no return." In such a situation, the artery-first PD is the choice of operation. Meticulous dissection of the SMA by the artery-first PD may increase margin negative rates and influence locoregional control [11].

Surgical Techniques

At our institution, we use the artery-first PD for all cases so that surgeons in training become familiar with the surgical principles and gain experience. The surgical techniques we use are presented here in detail.

Tora-no-Ana Approach

In the setting of pancreatic cancer, we utilize the "Tora-no-Ana" approach. In a Chinese text from the Han dynasty, there is a proverb: "One cannot get a tiger's cub without entering the tiger's lair." The term of Tora-no-Ana represents the tiger's lair in the Japanese language. Here, it also refers to an anatomic opening (= Ana) created by division of the ligament of Treitz (= Tora).

In the operating room, the operator stands on the right side of the patient, the first assistant stands on the opposite side, and the second assistant stands cranial to the operator (Fig. 14.2).

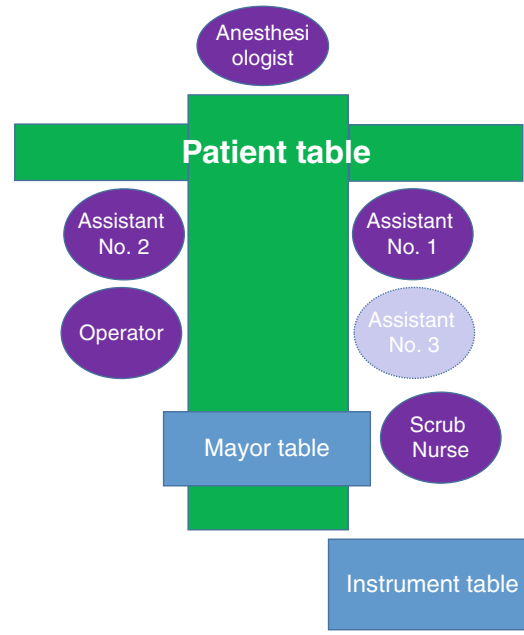

Fig. 14.2 Setting in operation room. A setting of the operation table, surgeons, scrub nurse, and anesthesiologist in the operation room. The assistant No.3 is optional

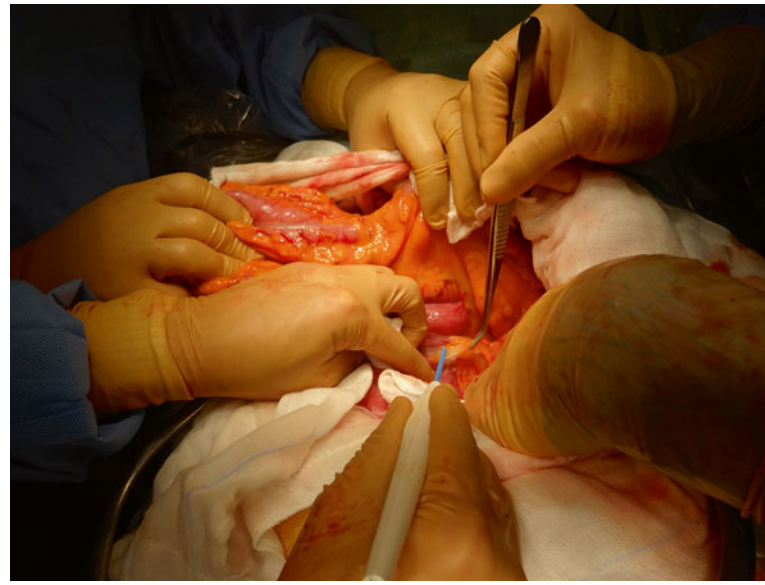

Fig. 14.3 Tora-no-Ana approach. The ligament of Treitz is divided along the lateral margin of the proximal jejunum, while the assistant surgeon retracts the transverse colon upward

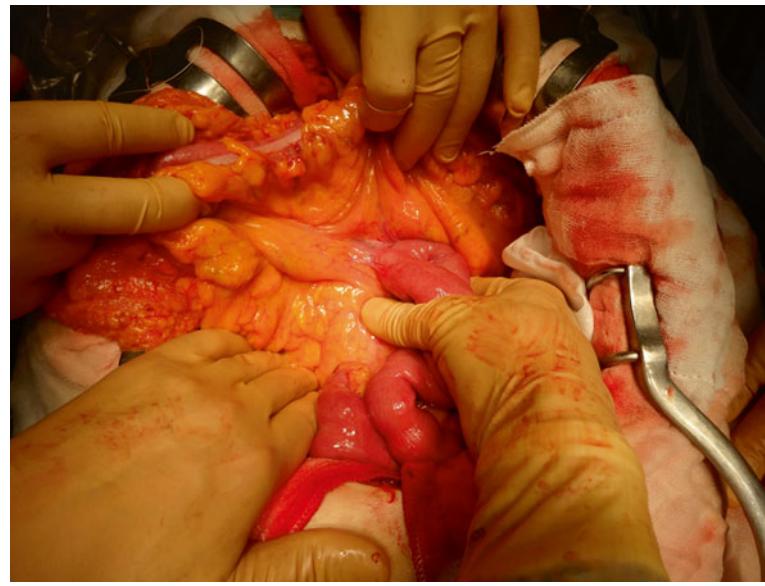

Fig. 14.4 Palpation of the superior mesenteric artery. The surgeon inserts his or her right four fingers into the Tora-no-Ana and palpates the superior mesenteric artery and its branches between the thumb and fingers

The transverse colon is lifted upward by an assistant surgeon and the ligament of Treitz is divided along the lateral margin of the upper jejunum (Fig. 14.3) and the retroperitoneal space is entered. Thus, the Tora-no-Ana is created and the para-aortic lymph nodes are sampled for frozen section. If needed, the inferior mesenteric vein (IMV) may be divided; the inferior posterior margin of the pancreatic body is then mobilized to open the Tora-no-Ana widely. Now, the surgeon can insert his or her right four fingers into the Tora-no-Ana and palpate the SMA and its branches by grasping the mesentery of the upper jejunum between the thumb and fingers (Fig. 14.4). In this way, the surgeon can locate the SMA no matter how obese the patient may be. During the procedure for further dissection, this palpation may be repeated so that the location of SMA is clearly identified.

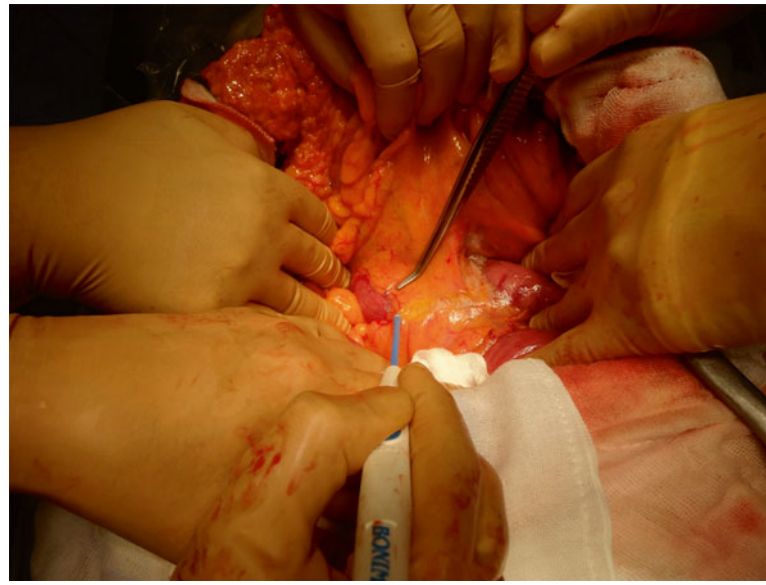

Fig. 14.5 Mesenteric approach. The peritoneum of the mesentery is divided between the inferior duodenal angle and proximal jejunum, while the assistant surgeon retracts the transverse colon upward

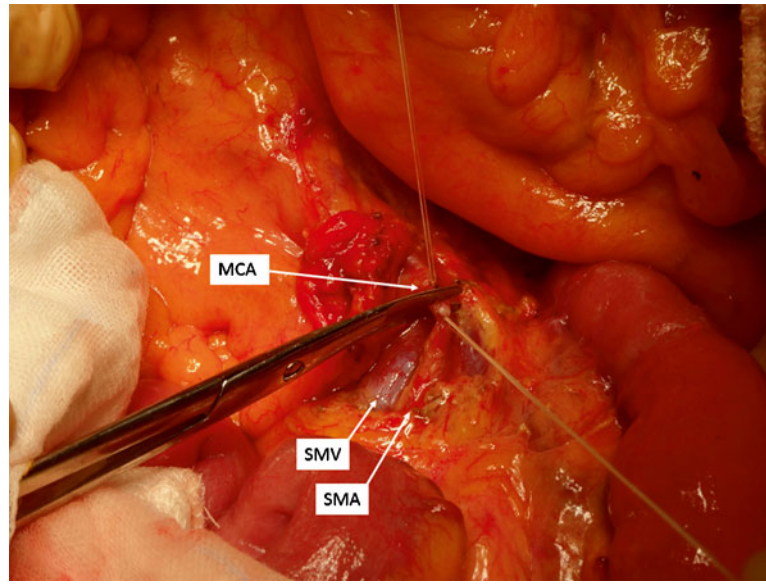

Fig. 14.6 Division of the middle colic artery. The middle colic artery (MCA) is divided close to the origin from the superior mesenteric artery (SMA). *SMV* superior mesenteric vein

The anterior peritoneum and adipose tissue of the mesentery is divided at the base of transverse mesocolon (Fig. 14.5). Usually, it is easier to first expose the SMV, which runs parallel to the SMA. The middle colic artery is divided at its origin for the better exposure of SMA (Fig. 14.6). It is important to identify the first jejunal vein in order to avoid incidental injury and bleeding. The SMV and first jejunal vein are looped (Fig. 14.7).

Division of the Transverse Mesocolon

The gastrocolic ligament is divided and the lesser sac is entered (Fig. 14.8). The middle colic vessels and right aberrant colic vessels are divided at their takeoffs from the inferior margin of the pancreatic body. The transverse mesocolon is widely divided along the anterior inferior margin of the pancreatic head and

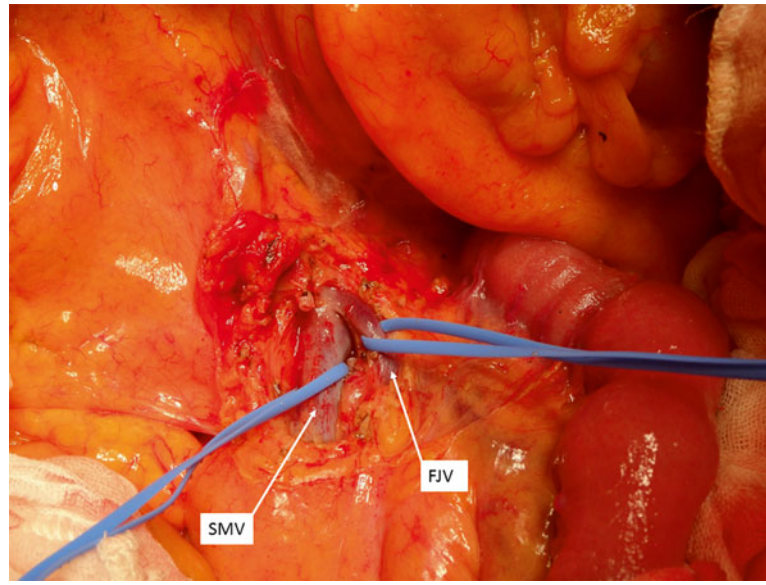

Fig. 14.7 Taping of the superior mesenteric vein and first jejunal vein. The superior mesenteric vein (SMV) and first jejunal vein (FJV) are exposed and taped at the base of transverse mesocolon

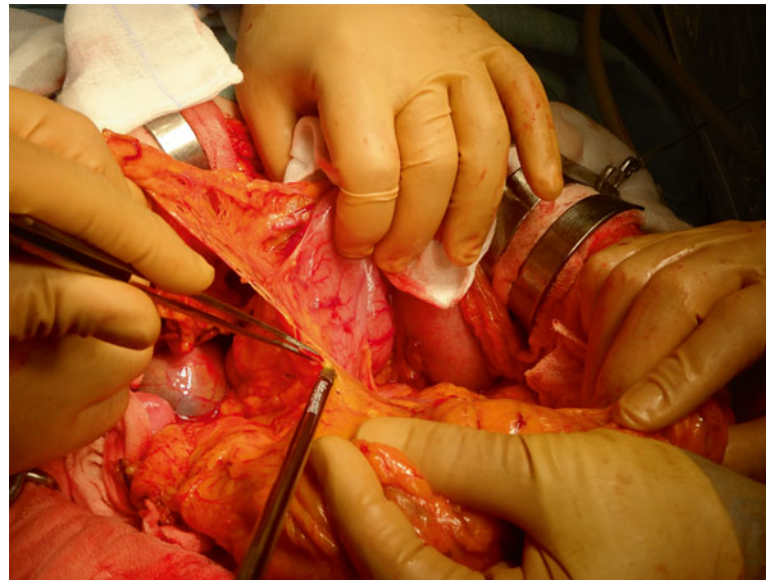

Fig. 14.8 Division of the gastrocolic ligament. The gastrocolic ligament is divided with a vessel sealing device and the lesser sac is entered. The superior mesenteric vein should not be exposed from the lesser sac or else the surgical margin may be compromised

body (Fig. 14.9). In this way, a part of the mesentery of transverse colon, where the head and proximal body of the pancreas are attached, is resected en bloc. In order to prevent ischemia of the colon, it is mandatory to exercise caution for preserving the arcade of vessels along the transverse colon.

Hanging Maneuver of the Pancreatic Body

After making a wide opening within the mesocolon, the transverse colon is retracted downward and the pancreas is well exposed. By retracting the stomach body upward, an avascular area on the left side

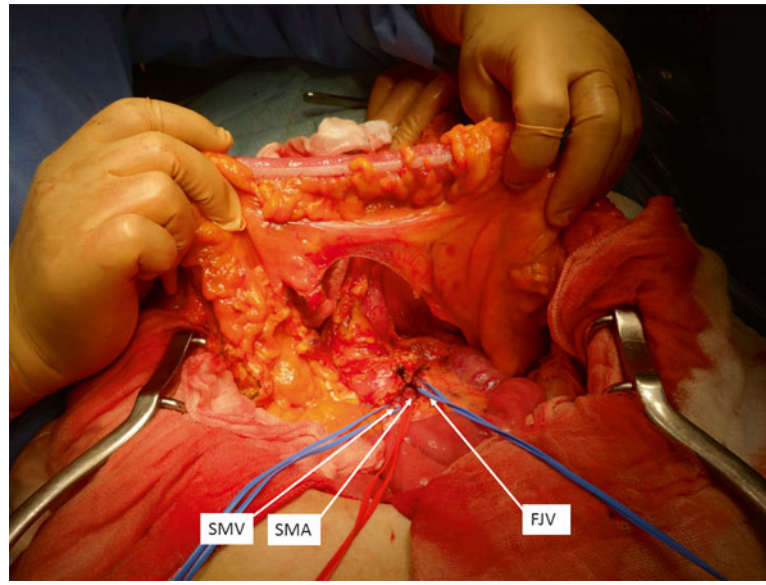

Fig. 14.9 Opening of the transverse mesocolon. The transverse mesocolon is divided along the anterior inferior margin of the pancreatic head and body and widely opened. *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *FJV* first jejunal vein

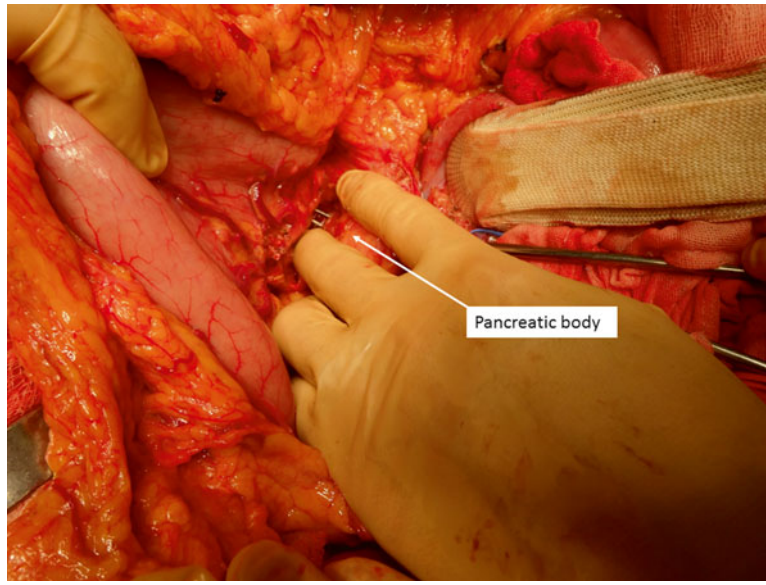

Fig. 14.10 Passage of large Kelly forceps toward avascular area above the splenic artery. Large Kelly forceps are inserted along the anterior wall of the superior mesenteric artery (SMA) into the space below the pancreatic body. Note that the forceps should be forwarded below the fusion fascia of Toldt. The large Kelly forceps are progressed toward the avascular area above the splenic artery until their tips appear above the pancreas and splenic artery. For easy passage, the avascular area located left to the origin of the left gastric artery and superior to the splenic artery may be dissected with a cautery prior to the passage of the large Kelly forceps

of the left gastric artery and superior to the splenic artery is dissected with a cautery for the preparation of later passage of a Penrose drain. Large Kelly forceps are inserted into the dissection plane between the pancreatic body and the SMA and are passed toward the avascular area that was dissected previously (Fig. 14.10). As long as the forceps are passed under the fusion fascia of

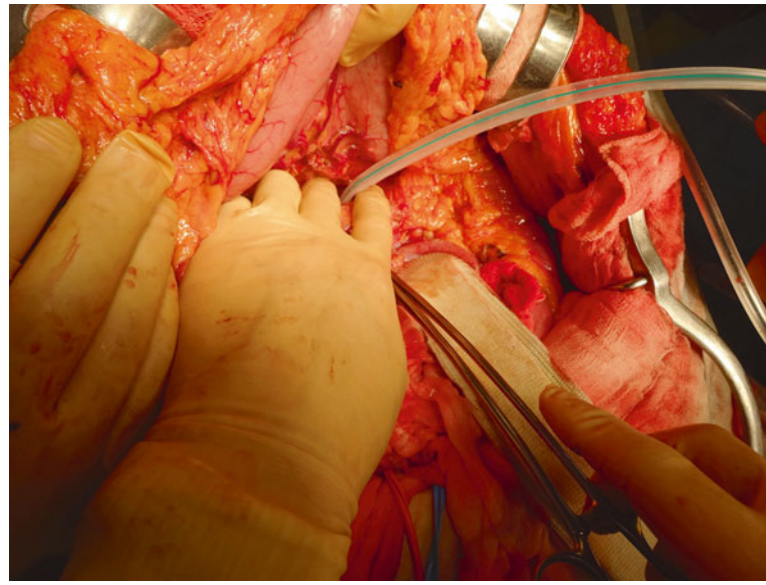

Fig. 14.11 Placement of Penrose drain for the hanging maneuver. A Penrose drain is placed by the large Kelly forceps. The Penrose drain encircles the pancreatic body, splenic artery and vein

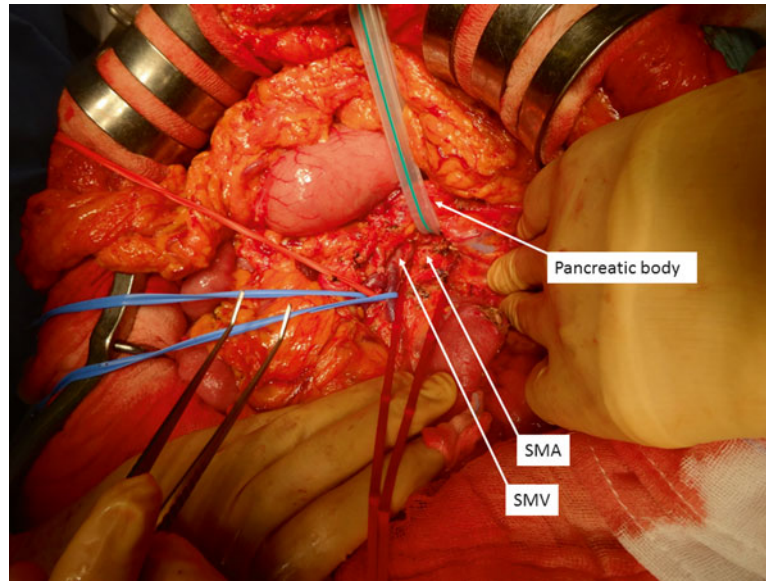

Fig. 14.12 Hanging maneuver. The pancreatic body is lifted upward by the Penrose drain. This hanging maneuver provides the surgeon with a better view of the proximal part of the superior mesenteric artery (SMA), where the inferior pancreaticoduodenal artery arises. *SMV* superior mesenteric vein

Treitz, they should meet no resistance. One should not attempt to progress the forceps between the pancreatic body and splenic artery, or an injury to the splenic vessels or dorsal pancreatic artery can result. A Penrose drain is passed with the large Kelly forceps (Fig. 14.11). A hanging maneuver is performed by lifting the Penrose drain cephalad, upon which hang the pancreatic body together with the splenic artery and vein (Fig. 14.12). With the hanging maneuver, the inferior vena cava is well exposed from the left side, and the left renal vein is exposed thorough the Tora-no-Ana.

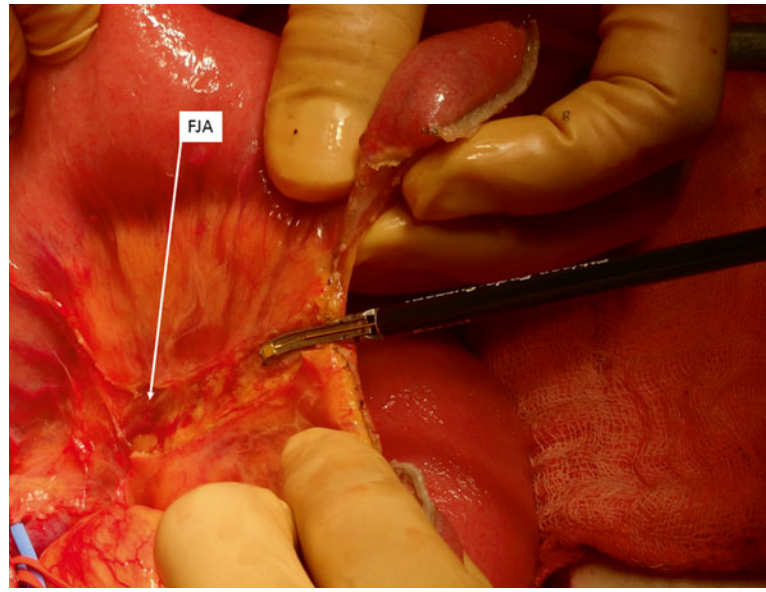

Fig. 14.13 Division of mesentery of the jejunum. After division of the upper jejunum with a linear stapler, the mesentery is divided along the first jejunal artery (FJA) with a vessel sealer

Division of Jejunum, First Jejunal Artery, and Inferior Pancreaticoduodenal Artery

The jejunum is divided with a linear stapler. In patients with locally advanced pancreatic cancer, the first jejunal artery is occasionally involved by the tumor. Moreover, it has been also reported that metastatic lymph nodes along the first jejunal artery may be present even in patients with resectable pancreatic cancer [12]. Therefore, we remove the proximal part of the first jejunal artery along with its associated lymph nodes. The mesentery is divided along the first jejunal artery (Fig. 14.13). The adipose tissue around SMA is cleaned circumferentially. Note that the nerve plexus around the SMA should be preserved. The first jejunal artery is divided at its origin from the SMA. The IPDA often forms a common trunk with the first jejunal artery [13] and may be divided at the trunk. If the IPDA has not been identified, the surgeon may retract the SMA anteriorly with tape and find the IPDA as a string arising from the posterior wall of the SMA toward the uncinate process of the pancreas; the IPDA is then divided at its origin (Fig. 14.14). In some patients, there are two IPDAs [13] and both of these are to be divided. If there is a branch from the SMA toward the pancreatic body, it should be divided as well. The IPDA arises from the SMA close to its root [13, 14], which is covered by the pancreatic body, and the hanging maneuver of the pancreatic body helps surgeons to identify the origin of IPDA.

Division of the Gastroduodenal Artery

A cholecystectomy is performed. The stomach is divided with a linear stapler. The proper hepatic artery, common hepatic artery, and GDA are looped (Fig. 14.15). In patients with borderline resectable pancreatic cancer extending toward the origin of GDA, the vascular wall of GDA may be fragile, especially after neoadjuvant chemoradiation. In such patients, we avoid ligation of the GDA because simple ligatures can collapse the wall of GDA instantly. Instead of ligatures, we occlude the common hepatic artery, proper hepatic artery, and GDA temporally with bulldog clumps, cut the GDA sharply with a surgical knife (Fig. 14.16), and treat the stump of GDA with a two-way running sutures of 6-0 Prolene.

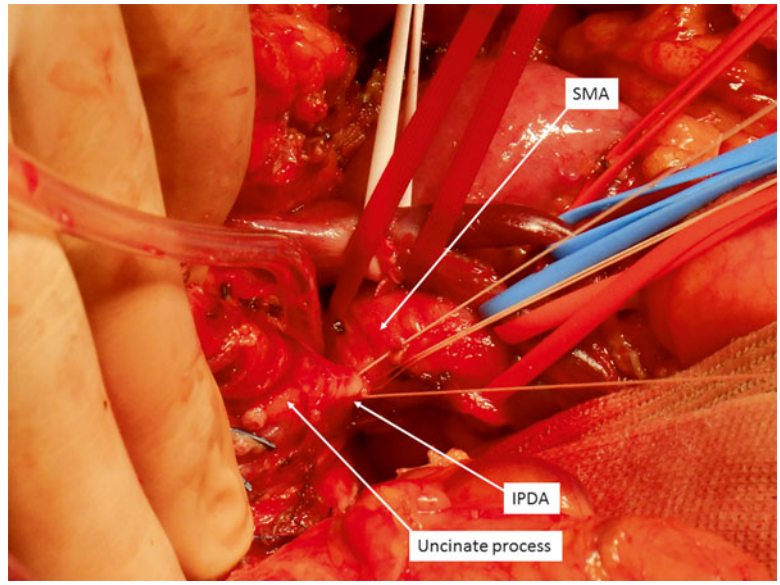

Fig. 14.14 Division of the inferior pancreaticoduodenal artery. The superior mesenteric artery (SMA) is retracted anteriorly and the inferior pancreaticoduodenal artery (IPDA) is identified as a string between the SMA and uncinated process

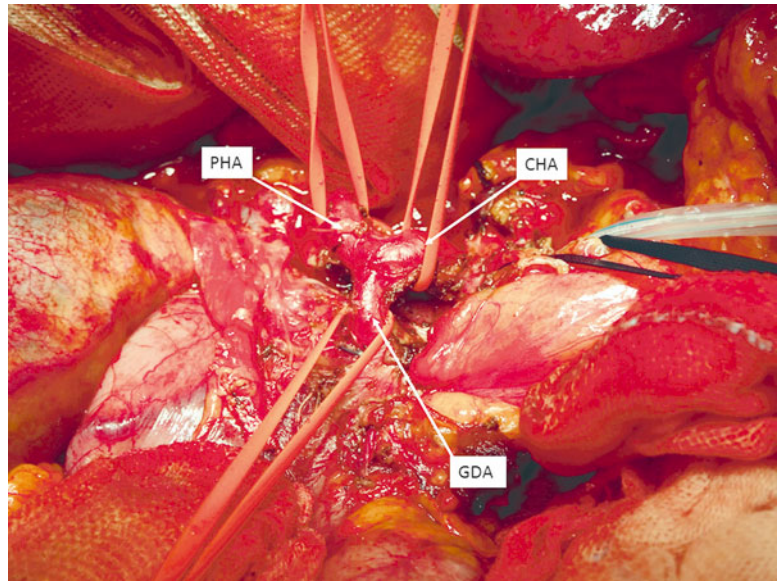

Fig. 14.15 Dissection around the gastroduodenal artery. The lymph nodes and adipose tissue around the common hepatic artery (CHA), proper hepatic artery (PHA), and gastroduodenal artery (GDA) are dissected and these arteries are taped individually

Division of the Pancreas

The splenic vein is taped and the Penrose drain for the hanging maneuver is now passed inside the splenic artery. The Penrose drain should now only hold the pancreatic body and splenic vein. We divide the pancreas along a transection line between the origin of the splenic artery and the left border of the SMA with cautery. The SMA margin is the most common site of a positive margin following PD, and we aim to remove the portion of the SMA margin en bloc with the entire specimen. Considering that there is a very small amount of pancreatic parenchyma between the portal vein and this transection line, removal of the pancreas to this extensive cutting line does

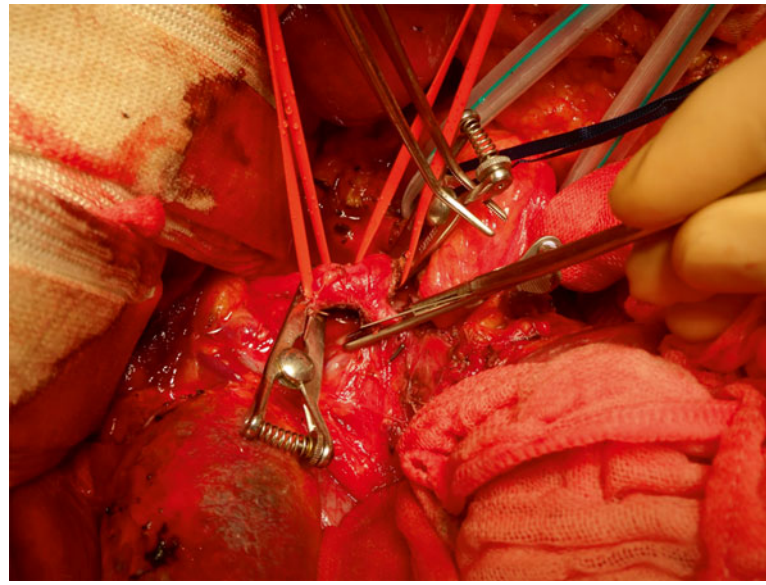

Fig. 14.16 Division of the gastroduodenal artery. The lymph nodes and adipose tissue around the common hepatic artery (CHA), proper hepatic artery (PHA), and gastroduodenal artery (GDA) are dissected and these arteries are taped individually

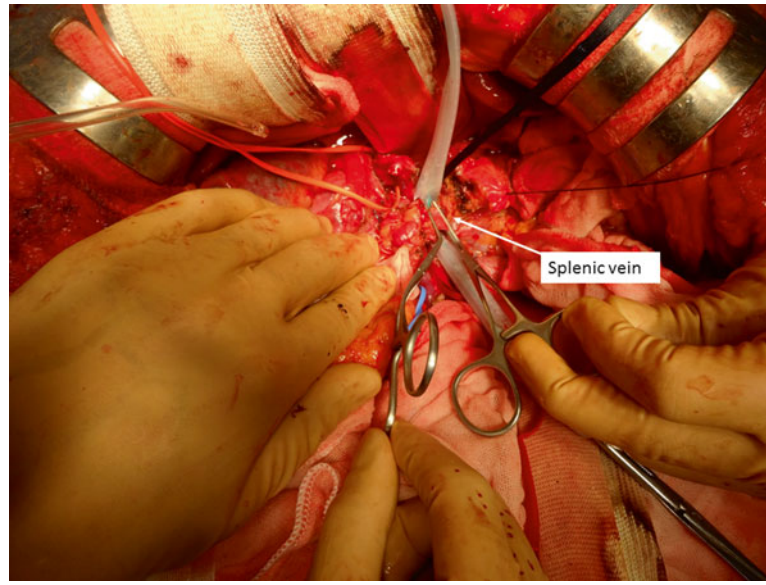

Fig. 14.17 Division of the splenic vein. After the division of the pancreatic parenchyma, the splenic vein is clumped with two pairs of Pots vascular forceps and divided

not adversely affect the endocrine and exocrine function of the remnant pancreas significantly. Strasberg and his colleagues advocate a Whipple procedure at the splenic artery, or WATSA [15], and we agree with their concept.

While dividing the pancreas, caution must be used to avoid injury to the splenic vein, which runs behind the pancreatic parenchyma. In cases requiring segmental resection of the SMV and portal vein, we do not attempt to free the splenic vein from the pancreatic parenchyma, but clamp and divide the splenic vein between two pairs of Potts vascular forceps after the division of pancreatic parenchyma (Fig. 14.17). The distal stump of splenic vein is closed with a two-way running suture of 6-0 Prolene.

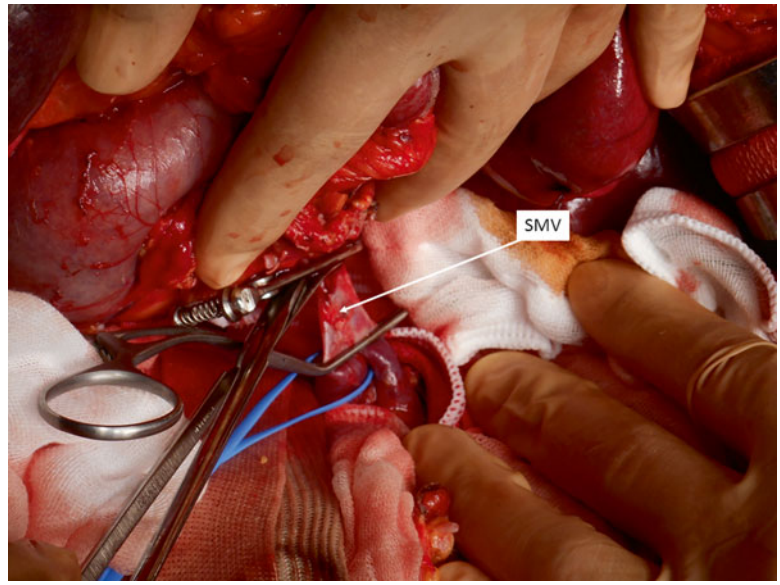

Fig. 14.18 Division of the superior mesenteric vein. The superior mesenteric vein (SMV) is clamped with Potts vascular forceps. The specimen side is also occluded with a bulldog clump to avoid contamination by the blood from the specimen. The SMV is divided along the bulldog. The portal vein (PV) is clumped with Pots vascular forceps and divided in the same way as the superior mesenteric artery (SMV) and the specimen is removed

Division of the Common Bile Duct

The common bile duct is divided cephalad to the confluence of the cystic duct. A drainage tube is inserted into the hepatic duct to contain bile drainage intraoperatively. When a metallic stent is placed preoperatively, the common duct is divided at the upper margin of the metallic stent, which we request be placed below the bifurcation of right and left hepatic ducts.

En Bloc Resection of the SMV and/or Portal Vein

The duodenum and upper jejunum is fully mobilized and retracted to the right side of SMA and SMV. The nerve plexus between the pancreas head and celiac artery is divided and the specimen is fully mobilized from all structures except the SMV and portal vein. The SMV and portal vein are serially divided between two pairs of Pots vascular forceps (Fig. 14.18) and the specimen is removed. The SMV and portal vein are anastomosed end-to-end with continuous sutures of 6-0 Prolene (Figs. 14.19 and 14.20). Interposition grafts are seldom necessary. When the confluence of SMV and splenic vein is involved by the tumor, the splenic vein is left divided and never reconstructed.

Discussion

Since March 2010, we have used this technique of artery-first PD routinely in patients who undergo a PD for pancreatic cancer. The artery-first PD has been successfully performed in all cases by surgeons, including less-experienced surgical staff and senior residents, under the supervision of the senior author. In fact, the intraoperative photographs used in this chapter were taken during an operation performed by young staff surgeons.

In our series, our R0 resection rate is 88 % and the average intraoperative blood loss is 1245 mL. The initial diagnoses of UICC Stage III and IV were made in 13 % and 5 % of patients, respectively, and the pathological T classification was T3 and T4 in 76 % and 1.3 %, respectively. Considering the high percentage of advanced disease, we are satisfied with the present data from our series. After 2010, the blood loss that occurred during operations we performed decreased in part

Fig. 14.19 End-to-end anastomosis of portal vein. The posterior walls of the superior mesenteric vein (SMV) and portal vein (PV) are approximated between the Potts vascular forceps and stitched with a continuous suture of 6-0 Prolene. Both edges of the posterior lip should be retracted bilaterally using a stay suture of 6-0 Prolene to prevent anastomotic stricture. The anterior walls of the superior mesenteric vein (SMV) and portal vein (PV) are approximated with a continuous suture of 6-0 Prolene

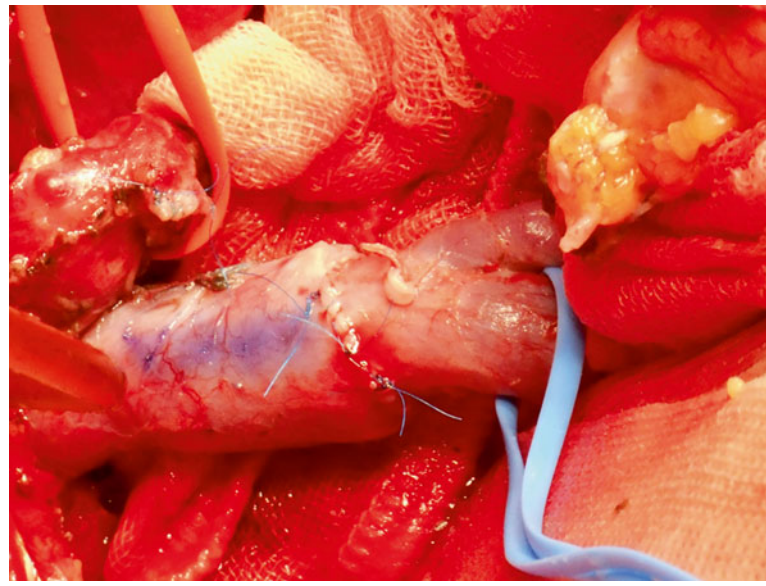

Fig. 14.20 End-to-end anastomosis of portal vein, completion. The end-to-end anastomosis of the superior mesenteric vein (SMV) and portal vein (PV) is completed

because we used new vessel-sealing energy devices. Therefore, it is difficult to evaluate how much the technique of artery-first PD directly contributed to a reduction in blood loss over time. It is also difficult to determine whether or not the artery-first PD contributed to improved survival through enhanced locoregional control. Randomized controlled trials are the only way to answer this question.

Based upon the results of previous randomized controlled trials comparing extended to standard dissections at PD [16], it is our present policy to preserve the nerve plexus around the SMA in order to avoid intractable diarrhea. In case of suspected invasion into the nerve plexus, we use neoadjuvant intensity-modified radiation therapy in combination with full-dose gemcitabine with the goal of "sterilizing" the cancer cells in this location.

By preserving the nerve plexus around the SMA, we have been able to manage postoperative diarrhea with loperamide and/or tannic acid in all patients.

Following neoadjuvant chemoradiation, inflammatory reactions and adhesions may develop in the irradiated tissues. Such changes may make surgical dissection more difficult. In such a challenging situation, the artery-first PD may help surgeons to reduce blood loss and to develop the appropriate dissection plane. The highest BMI in our series was 35.2 %. By using the Tora-no-Ana approach, the SMA was easily palpable even in the obese patients. The hanging maneuver of the pancreatic body also helps surgeons to establish a good operative field around the origin of SMA. In conclusion, our technique of artery-first PD is feasible if the surgical principles of the Tora-no-Ana approach are followed.

Acknowledgement The authors have no conflicts of interest to disclose.

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15 Venous Shunting Procedures for Borderline Resectable Pancreatic Cancer

Amir H. Fathi, Susan Tsai, Jeffrey E. Lee, Douglas B. Evans, and Kathleen K. Christians

Introduction

Historically, involvement of the PV or SMV by pancreatic cancer was a contraindication to PD [1]. However, in 1963 the concept of "regional pancreatectomy" was introduced by Asada, and subsequently Fortner and colleagues [2, 3] in which systematic resection of major peripancreatic vascular structures and wide soft tissue clearance was performed. Resection of the PV at the time of PD as part of regional pancreatectomy was completed with the intention of improving survival [1, 2]. However, this form of extended PD to include routine PV resection failed to achieve this goal [4–6]. Importantly, those patients who underwent regional pancreatectomy were not selected utilizing the rigor of contemporary imaging studies and did not receive multimodality therapy. In contrast to regional pancreatectomy, contemporary vascular resection/reconstruction is performed when the operating surgeon cannot safely separate the PV, SMV, or the SMV–PV confluence from the tumor; it is not performed for the purpose of achieving a wider soft tissue clearance [7]. At present, resection and reconstruction of the PV–SMV confluence during PD is associated with a low rate of perioperative morbidity and similar rates of R0 resection and overall survival as compared to patients who undergo standard PD without venous resection [7, 8].

Emerging systemic therapies have improved the magnitude of treatment responses leading to a new era in the operative management of exocrine and endocrine carcinoma of the pancreas. With more accurate staging and more effective systemic therapies, patients who are potential candidates for pancreatectomy in combination with complex vascular resection are being seen with increasing frequency [9, 10]. Patients who have evidence of clinical benefit (improved symptoms and/or performance status), radiographic response (stable or responding disease on cross-sectional imaging), and a decline in available tumor markers (CA19-9, carcinoembryonic antigen) represent the optimal patient subset to consider extended, high-risk operations.

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Exposure of the SMA

The most critical oncologic step during PD for pancreatic cancer is the dissection of the SMA [8, 10]. Adequate exposure of the SMA is essential to completing a safe dissection and facilitating a negative margin. When tumors are inseparable from the SMV or the SMV–PV confluence, SMA exposure is traditionally accomplished by one of the two following techniques [11]:

1. Medial to lateral approach
   As originally described by Fortner, the SMA can be exposed medial to the SMV if the SMV–PV confluence is encased at the splenic vein (SV) confluence [2, 12]. Division of the SV allows for wide exposure of the SMA and also facilitates resection and reconstruction of the SMV–PV confluence as the PV is no longer tethered by the SV confluence. SV division permits a direct anastomosis between the SMV and PV, usually without the need for interposition grafting (adequate length is usually not problematic in this situation). Importantly, division of the SV provides access to the proximal SMA and celiac axis, which greatly facilitates tumor separation from these visceral arteries. However, if the inferior mesenteric vein (IMV) enters the SMV instead of the SV (Fig. 15.1), SV ligation may predispose to sinistral portal hypertension and gastrointestinal hemorrhage as retrograde decompression through the IMV is not possible (Fig. 15.2). In such cases, the authors prefer distal splenorenal shunting (DSRS) to decompress the splenic vein.
2. Artery first approach
   If the segment of SMV to be resected is distal to the SV–PV junction, the SV does not need to be divided. However, preservation of the SV (a) prevents easy access to the proximal SMA anteriorly and (b) usually necessitates interposition grafting, as the PV remains teth-

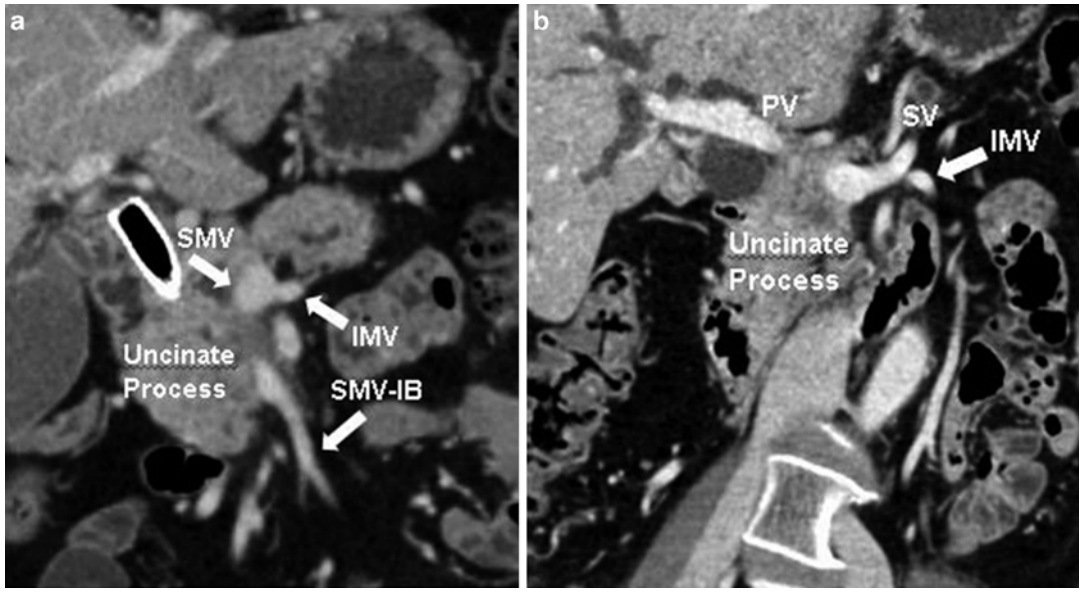

Fig. 15.1 (**a**, **b**) Coronal CT images of anatomic variations of the IMV insertion site. In Fig. 15.1a, the IMV drains into the SMV (*Arrow*) whereas in Fig. 15.1b, the IMV drains into the SV (*Arrow*). In the first scenario, if SV ligation is required to remove the SMV–PV confluence due to tumor abutment/encasement at the time of pancreaticoduodenectomy, there is no avenue for retrograde decompression of the SV other than through collaterals. This may result in sinistral portal hypertension. Alternatively, as seen in Fig. 15.1b, if the SV is ligated at the PV–SMV–SV confluence, the IMV may provide retrograde decompression of the SV. *SMV-IB* superior mesenteric vein's iliac branch, *IMV* inferior mesenteric vein, *SMV* superior mesenteric vein, *PV* portal vein, *SV* splenic vein

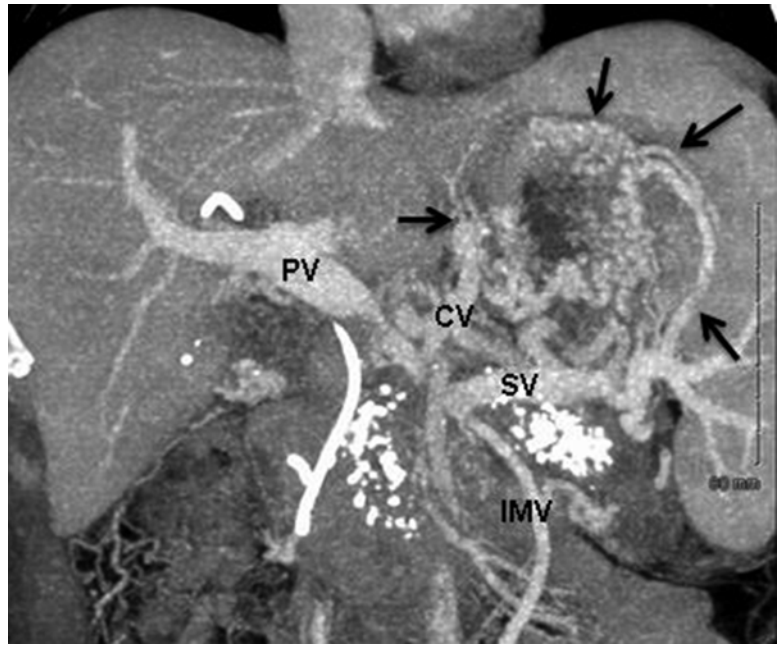

Fig. 15.2 Coronal CT venous reformatted images illustrating development of sinistral portal hypertension in a patient with chronic pancreatitis. In this patient, the PV–SMV is focally occluded and gastric varices have developed. Ligation of the SV at the confluence will only worsen this situation as the IMV will also be sacrificed. *Arrows* point to extensive left-sided portal hypertension. Coronary vein (CV) is significantly enlarged. *PV* portal vein, *SV* splenic vein, *IMV* inferior mesenteric vein

ered at the PV–SMV–SV confluence thereby preventing the PV from having enough length to complete a primary anastomosis to the SMV. For these two reasons, some surgeons routinely divide the SV when performing segmental venous resection and reconstruction. Preservation of the SV–PV junction is important because it essentially eliminates the risk of PV thrombosis or stenosis. Alternatively, when resecting the SMV distal to the splenic-portal junction, the tumor can be separated from the SMA first, as initially described by Leach and colleagues [13]. This approach is technically challenging and is appropriate only for modest-sized tumors with short-segment SMV encasement (Fig. 15.3).

Venous Shunting Procedures

Mesocaval Shunts

An additional technique that can be used when SMV resection is required includes the creation of a mesocaval shunt. Read and colleagues first described the use of homologous vein graft as a conduit for the mesocaval shunt in 1970 [14]. Drapanas popularized the procedure for the treatment of portal hypertension in 1972 by showing efficacy in 25 patients with acute exsanguinating variceal hemorrhage. Throughout the 1970s, several authors reported success with autologous, homologous, heterologous, and synthetic mesocaval shunts for the treatment of portal hypertension and bleeding gastroesophageal varices [15]. In addition, in 2002, Orloff and coworkers published a series of 200 patients with extrahepatic portal hypertension secondary to portal vein thrombosis, who were successfully treated with portosystemic shunts. All of these patients had normal liver biopsies with normal liver function, and the majority of patients underwent mesocaval shunts with no immediate postoperative mortality [16].

We first used temporary mesocaval shunting during PD in patients with radiographic evidence of cavernous transformation of the PV due to short-segment SMV–PV occlusion. When the pancreatic head is removed in the setting of PV/SMV occlusion, collateral flow is eliminated and therefore, there is no venous outflow for the midgut. In such cases, the portal dissection should not be attempted until portal flow is diverted due to the risk for life-threatening hemorrhage if these collaterals (especially in the porta hepatis) are inadvertently entered. In the setting of

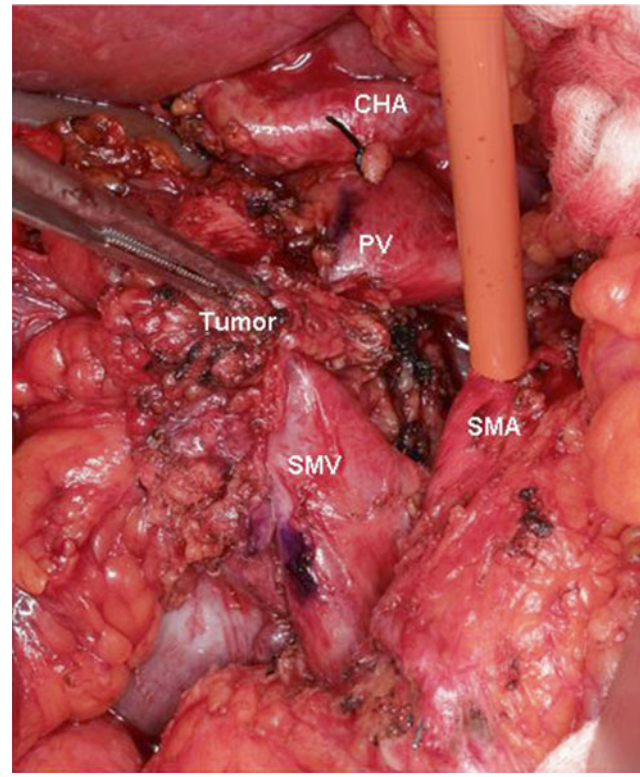

Fig. 15.3 Intraoperative photograph of a SMA first approach. A modest-sized tumor with short-segment SMV encasement is separated from the SMA by an artery-first dissection leaving the tumor/specimen attached only to the PV–SMV confluence. A Rommel tourniquet is seen encircling the SMA to provide inflow occlusion during venous resection and reconstruction thereby decreasing bowel wall edema. *PV* portal vein, *SMV* superior mesenteric vein, *CHA* common hepatic artery, *SMA* superior mesenteric artery

cavernous transformation of the PV, PD with venous reconstruction requires an appropriate length of the SMV below (usually the main concern) and PV above the region of tumor encasement.

In addition to reducing blood loss during the dissection, temporary mesocaval shunting greatly enhances the exposure of the entire root of mesentery. Therefore, we have expanded the indications for mesocaval shunting to include patients who not only require a difficult SMV resection/reconstruction, but also those who pose a challenging SMA dissection. For example, when the tumor encases the SMV and abuts the SMA (often the posterior wall of the SMA and usually accompanied by tumor extension into the root of the small bowel mesentery), optimal SMA exposure is an absolute necessity. In such situations, we have divided the SMV and used an internal jugular vein (IJV) as an autologous interposition graft to create a temporary mesocaval shunt from the SMV to the inferior vena cava (IVC). In contrast to the previously discussed technical options for SMA exposure (medial to lateral, and artery first), this technique allows for wide exposure of the root of the mesentery and prevents any form of traction injury on the SMV–PV confluence during the SMA dissection (Fig. 15.4). These operations represent the highest level of technical complexity and are only offered to very carefully selected patients, and always after a period of induction therapy when performed for pancreatic adenocarcinoma.

Surgical Technique for Mesocaval Shunt

The initial steps of PD are performed as previously described by Evans and colleagues [11, 17]. CT evidence of tumor involvement of the SMV or its first-order branches should prompt thorough scrutiny of the venous anatomy to determine the extent of vascular involvement and to develop an optimal strategy for vascular resection and reconstruction. High-quality preopera-

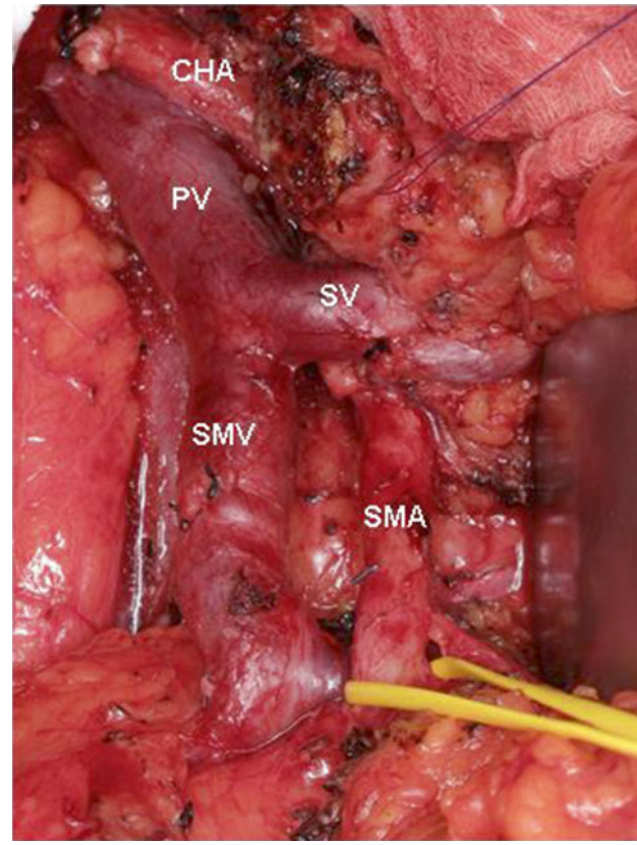

Fig. 15.4 Intraoperative photograph of a mesenteric root dissection. This maneuver provides wide exposure of the SMA and prevents any form of traction injury on the SMV–PV confluence during SMA dissection. In this image, the SMV and SMA are completely skeletonized and the SMA is encircled by a vessel loop. *PV* portal vein, *CHA* common hepatic artery, *SV* splenic vein, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery

tive CT imaging should prevent unexpected venous resections at the time of PD.

The SMV caudal to the area of tumor encasement should be exposed and this part of the operation is extremely difficult when tumor extends into the transverse mesocolon. The SMA dissection is critical and exposure of the SMA medial to the SMV early in the operation is strongly encouraged. Extended kocherization of the duodenum to the left lateral border of the aorta exposes the anterior surface of the left renal vein (and the location of the SMA origin can usually be appreciated at this time). An autologous left internal jugular vein (IJV) conduit is harvested to create the mesocaval shunt. The IJV graft should be marked along its anterior surface, prior to harvest, to prevent a twist during creation of the anastomoses. The IJV graft-caval anastomosis is performed first to minimize arterial inflow-occlusion time. When the first anastomosis is complete (Fig. 15.5a), we usually deliver a modest dose (2000 IU) of systemic heparin as the SMA will be temporarily occluded with a Rommel tourniquet. This technique allows arterial inflow occlusion to be limited to less than 15 min while the second anastomosis (SMV–IJV) is performed. Systemic heparinization is not mandatory and we use heparin only when the remaining dissection will not be significantly complicated by the use of anticoagulation. We divide the SMV just cephalad to its bifurcation into the jejunal and ileal branches. Whenever possible we try to preserve the jejunal branch, but if necessary, it can be divided. The IJV–SMV anastomosis completes the mesocaval shunt, connecting the SMV cephalad to its jejunal-ileal bifurcation to the IJV which is connected to the IVC (Fig. 15.5a). The anastomoses are completed end-to-end with interrupted 6-0 prolene sutures. Creation of the SMV–IJ–IVC mesocaval

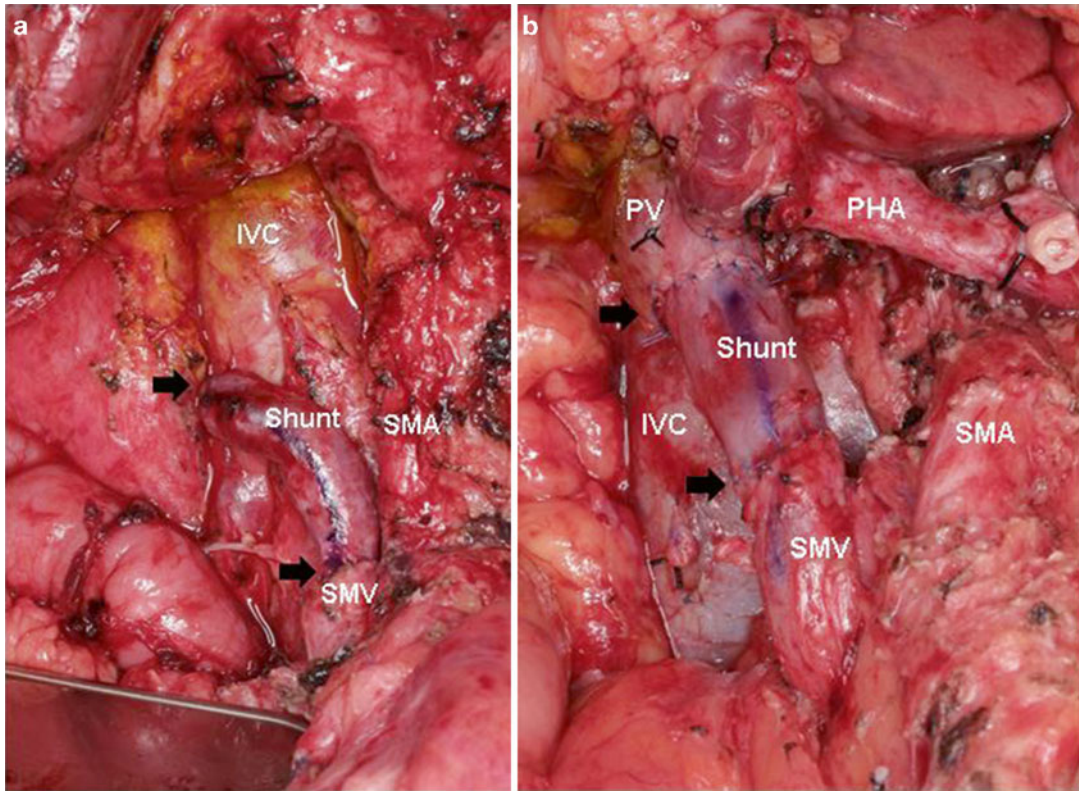

Fig. 15.5 (**a**) Intraoperative photograph of a mesocaval shunt in place, connecting proximal SMV to IVC via an autologous IJ vein graft. (**b**) is an intraoperative photograph of a completed mesoportal shunt (SMV–IJ–PV), demonstrating the final vascular reconstruction after specimen extraction (*arrows* point at anastomoses). *SMA* superior mesenteric artery, *PHA* proper hepatic artery, *IVC* inferior vena cava, *SMV* superior mesenteric vein, *PV* portal vein, *IJ* internal jugular interposition graft

shunt will completely expose the root of the small bowel mesentery and provides excellent SMA exposure. Once all portal flow is diverted, the portal dissection can then be safely completed and the PV at the superior border of the pancreas is divided with an endovascular GIA stapler. The specimen is then removed and sent to pathology. The IVC–IJV end of the mesocaval shunt is then detached, cut to the appropriate length, and anastomosed to the PV forming the final interposition graft anastomosis (Fig. 15.5b).

If the SMA required skeletonization accompanied by complete resection of the root of mesentery, we have occasionally covered the SMA to prevent access of a pancreatic anastomotic leak to the artery itself. In this setting, we have used spiral vein graft reinforcement of the SMA incorporating autologous saphenous vein. The saphenous vein is dilated with heparinized saline, opened longitudinally and sewn around the exposed SMA in a spiral manner to reinforce any arteriotomy closures at the sites of the pancreaticoduodenal and/or jejunal branches that required excision.

Distal Splenorenal Shunt

To achieve an R0 resection in cases of borderline resectable pancreatic cancers, SV ligation may be necessary when tumor encasement of the SMV–PV confluence occurs at the junction of the SV. As described by Misuta and colleagues, the IMV enters just at, or inferior to the SMV–PV confluence (directly into the SMV) in approximately 30 % of patients, such that the IMV will

not allow for retrograde decompression of the SV [18]. In this situation, retrograde decompression of the SV into the IMV will not occur as the IMV–SV confluence either did not exist or could not be preserved. This can result in increased flow through gastric and esophageal veins, causing sinistral portal hypertension with the risk of gastrointestinal hemorrhage (Fig. 15.2). Sinistral portal hypertension may also cause some degree of hypersplenism, resulting in thrombocytopenia. Even if the drop in platelet count is mild, this may significantly complicate the delivery of cytotoxic chemotherapy in the adjuvant setting or in the event of disease recurrence.

The physiologic significance of SV ligation remains a controversial topic. Authors who agree that SV ligation can be performed without concern for late complications have demonstrated in small series that the pattern of collateralization is not always through the stomach and esophagus, but also may occur through the colon, omentum, or other adjacent vessels. Therefore, gastrointestinal bleeding is not common in their experience [19]. However, proponents of the theory of sinistral portal hypertension after SV ligation have recommended reimplantation of the SV into the SMV–PV confluence or into the IMV when the SV–IMV junction is not intact [18, 20]. These series have demonstrated retrograde venous flow through the IMV after SV ligation in the setting of an intact SV–IMV junction. Similar to Misuta and colleagues, we believe that in patients who require SV ligation and who do not have an intact SV–IMV junction, reimplantation of the SV is required to avoid the risk of subsequent gastrointestinal hemorrhage [18]. However, we do not advocate reimplantation of the SV back into the reconstructed SMV–PV confluence because this may cause distortion of the SMV–PV anastomosis (after either resection and primary repair, or interposition grafting). An alternative technique for SV decompression is to use the left renal vein otherwise known as a distal splenorenal shunt (DSRS), first popularized by Dr. Dean Warren [21]. A DSRS is technically easier to perform compared to other anastomoses of the SV (to IMV or reconstructed SMV–PV) and provides a large outflow vessel, theoretically negating the potential "upward flow" phenomena described by Misuta et al. [18].

Surgical Technique for Distal Splenorenal Shunt

The DSRS was utilized by Warren and colleagues in 1969 for selective variceal decompression, to prevent recurrent variceal bleeding in the setting of portal hypertension [21, 22]. We have extrapolated the use of this technique to instances where the IMV enters the SMV and therefore, would not serve to decompress the SV after ligation of the distal SV. When a DSRS is created at the time of PD, the initial steps of PD are performed as previously described. The pancreas is divided at, or to the left of the SMV–PV–SV confluence, taking care to preserve the SV. The pancreatic body is elevated up and off of the SV by ligating small venous tributaries to the pancreas. Posterior and slightly inferior to the SV, the left renal vein is exposed. The left adrenal vein may be ligated and occasionally, this area of the left renal vein has been incorporated into the venotomy to create an optimal anastomotic site in the left renal vein. The SV is then sutured to the left renal vein in an end-to-side fashion with a posterior running suture of 6-0 prolene and an anterior row of interrupted 6-0 prolene sutures [10, 18] (Fig. 15.6).

Summary

The historic aspects and technical details of vascular resection/reconstruction and mesenteric shunting during PD have been reviewed. Venous shunting strategies provide wide exposure of the root of mesentery and can divert portal flow in select patients who require either venous reconstruction in the setting of cavernous transformation of the PV and/or a challenging SMA or celiac dissection. These techniques optimize one's ability to achieve a negative margin of resection and add an element of safety to an otherwise technically complex operation.

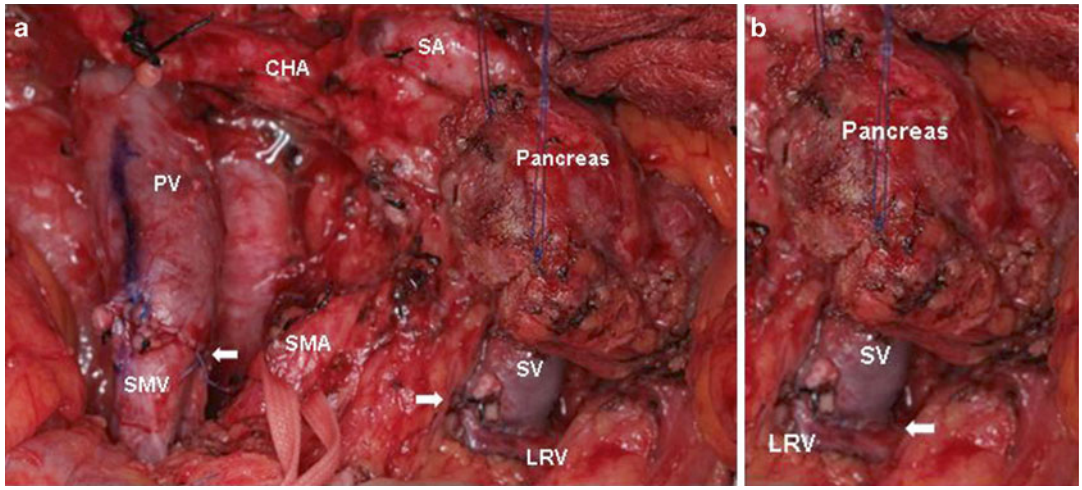

Fig. 15.6 (**a**) Intraoperative photograph of a completed SMV–PV resection with primary anastomosis and distal splenorenal shunt. (**b**) is a magnified view of the distal splenorenal shunt (*arrows* point at anastomoses). *SA* splenic artery, *CHA* common hepatic artery, *LRV* left renal vein, *SV* splenic vein, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *PV* portal vein

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16 The Role of the Appleby Operation and Arterial Resection in the Multimodality Management of Borderline Resectable Pancreatic Cancer

Ken-ichi Okada and Hiroki Yamaue

Introduction

The application of distal pancreatectomy with celiac axis en bloc resection (DP-CAR)—the so-called *modified Appleby operation* for borderline resectable pancreatic body/tail carcinoma—remains controversial because few studies have rigorously assessed the indications for and outcomes associated with this technique. One of the purported advantages of the procedure is the ability to widely clear tissues behind a tumor by the division of the root of the celiac axis. Another purported advantage is its impact on cancer pain arising from tumor invasion into the nerve plexus.

Recently, long-term survivors have been reported following the modified Appleby operation (DP-CAR) [1]. A median survival time of 9.5–12 months was reported in a separate analysis of 43 patients [2]. It is accepted that margin-negative (R0) resection is generally necessary to achieve these favorable postoperative outcomes. However, the status of the surgical margins is not the only consideration with regard to the survival of patients with advanced disease. Indeed, tumors involving arterial structures often recur rapidly—even after an apparent R0 resection. Therefore, the aggressive systemic tumor biology associated with these cancers must be critically considered prior to contemplating the potential benefits of this radical surgery. In this regard, the Appleby operation may best be utilized following effective systemic neoadjuvant therapy.

History and Background of the Appleby Operation for Pancreatic Cancer

In 1973, Fortner introduced the regional resection of pancreatic cancer with major vascular en bloc resection as a new approach [3] to treat patients with localized pancreatic cancer. In his report, 8 of the 15 individuals (53 %) who survived his operation lived for periods ranging from 4 to 17 months after surgery. Six lived more than 1 year after regional pancreatectomy. Actual survival by Kaplan–Meier estimate was 62 % at 1 year, compared with a 36 % 1-year survival rate for a group of 17 patients who underwent pancreaticoduodenectomy for less advanced cancers at the same institution from 1959 to 1969 [4]. The described approach appeared to yield the greatest potential benefit in patients with small pancreatic cancers, which could be resected with wide margins.

The Appleby operation was first reported as a resection of the celiac axis for complete lymphadenectomy in a radical resection of gastric carcinoma in 1953 [5, 6]. In 1976, Nimura et al. [7]

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reported adapting the Appleby operation for resection of pancreatic body/tail tumors involving the celiac axis and/or the common hepatic artery (CHA). In 1991, Hishinuma et al. [8] modified this procedure to preserve the entire stomach, which improved postoperative nutritional status and quality of life. In 2000, Konishi et al. [9] reported reconstruction of the hepatic artery when pulsation in the proper hepatic artery (PHA) was weak after test occlusion of the celiac axis.

Since then, several institutions have reported their experiences with the modified Appleby operation for advanced pancreatic body/tail carcinoma (i.e., distal pancreatectomy combined with celiac axis en bloc resection, referred to as DP-CAR by Kondo et al. [10]). Despite reports of a few long-term survivors, the overall survival benefit and the risks of this challenging operation are unknown because previous reports have included small numbers of patients [11–14]. In the era of borderline resectable pancreatic carcinoma [15–24], this procedure has once again attracted pancreatic surgeons' attention as a method for radical pancreatectomy for borderline resectable cancers of the pancreatic body and/or tail.

The Anatomical Features of the Celiac Trunk and Its Branches

In 1917, Eaton reported that the most common celiac axis anatomy features the left gastric artery (LGA) as a collateral branch before the bifurcation into the hepatic and splenic arteries (62.1 % of 541 cases), while a true trifurcation occurs with somewhat less than half the frequency (24 % of 541 cases) [25]. More recently, the celiac was found to bifurcate into the splenic and the common hepatic artery (CHA), with the left gastric artery (LGA) originating as a first branch from the celiac trunk, in 72 % of 90 cadavers [26]. Malnar et al. [26] described the length of the celiac trunk (measured by a vernier caliper) as varying between 1.0 and 3.5 cm from its origin to the point where main branches occur. They reported that the length was 1.9 ± 0.08 cm if a trifurcation was present, while with a bifurcation, the length was 2.0 ± 0.08 cm. Among the celiac trunk normal main branches, the splenic artery had the largest diameter (0.61 ± 0.05 cm), the mean arterial diameter of the CHA was intermediate (0.57 ± 0.04 cm), and the LGA had the smallest diameter (0.38 ± 0.03 cm) [26–29].

The Organs and Tissues Resected with the Modified Appleby Operation (DP-CAR)

As initially described by Hirano et al. [1], the modified Appleby operation routinely includes en bloc resection of the celiac, common hepatic, and left gastric arteries; the celiac plexus and ganglions; the nerve plexus around the superior mesenteric artery; a part of the crus of the diaphragm and the Gerota fascia; the left adrenal gland; the retroperitoneal fat tissues containing lymph nodes above the left renal vein; the transverse mesocolon covering the body of the pancreas; and the inferior mesenteric vein. Resection of the portal vein and the middle colic vessels is optional. In general, no reconstruction of the arterial system is required because of early development of the collateral arterial pathways via the pancreatoduodenal arcades from the superior mesenteric artery. Preoperative coil embolization of the common hepatic artery may be used to enlarge the collateral pathways and prevent ischemia-related complications. In addition, because the stomach is preserved, no reconstruction of the alimentary tract is required. Based on the anatomical features and the relationship between the tumor and artery, the LGA and inferior phrenic arteries can generally be preserved. Table 16.1 describes the organs, vessels, and other tissues that are resected and preserved in this procedure. Figure 16.1 shows the surgical field after the modified Appleby operation (DP-CAR).

Table 16.1 The organs, vessels, and other tissues that are resected and preserved in the modified Appleby operation (DP-CAR)

	Resection	Preservation	Optional resection
Organ	Pancreas (body/tail), left adrenal gland, gallbladder[a], spleen	Stomach, duodenum	
Vessels	Celiac artery, common hepatic artery, splenic artery, dorsal pancreatic artery, short gastric vessels, posterior gastric artery, inferior mesenteric vein.	Inferior pancreaticoduodenal artery, gastroduodenal artery (pancreatoduodenal arcades), proper hepatic artery, the right gastric and right gastroepiploic vessels, gastrocolic trunk	Portal vein, middle colic vessels. Left gastric artery[a] [30] and inferior phrenic arteries can be preserved based on the anatomical features.
Other tissues	Part of the crus of the diaphragm, the Gerota fascia, the celiac plexus and ganglions, the nerve plexus around the superior mesenteric artery, the retroperitoneal fat tissues bearing lymph nodes above the left renal vein, the transverse mesocolon covering the body of the pancreas	Right adrenal gland, bilateral kidneys	

[a]Several institutions routinely perform resection

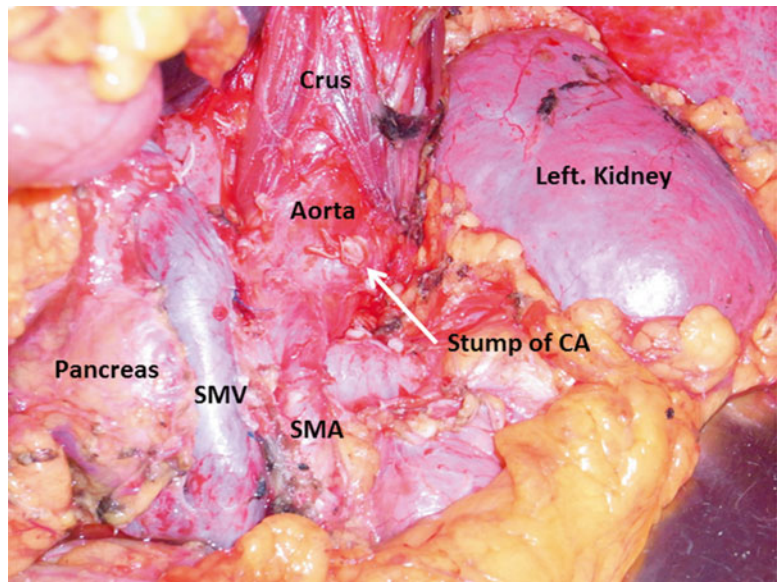

Fig. 16.1 The surgical field after the modified Appleby operation (DP-CAR). *CA* celiac axis, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery

Indications for the Modified Appleby Operation (DP-CAR) in Patients with Pancreatic Body/Tail Carcinoma

The modified Appleby operation should be performed in institutions with well-trained and experienced staff. When it was initially introduced, this procedure was indicated for patients with pancreatic body/tail carcinoma involving the celiac axis and/or CHA (Fig. 16.2). Recent literature has reported that this procedure can be used for patients with pancreatic body/tail tumors that involve or approximate at least one of the common hepatic arteries, the root of the splenic artery, or the celiac axis [1] (Fig. 16.2). This finding implies that this procedure may also

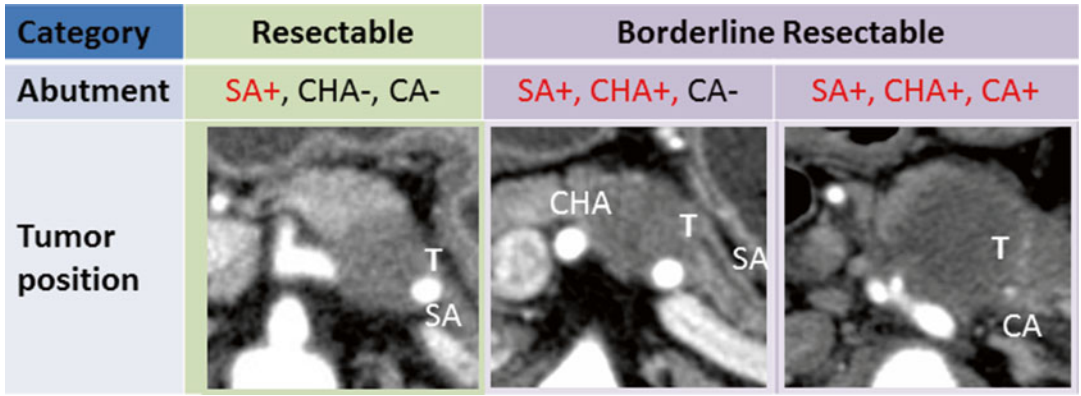

Fig. 16.2 The association between the category of resectability and the tumor abutment of the celiac axis and its branches with imaging of computed tomography. *SA* splenic artery, *CHA* common hepatic artery, *CA* celiac axis

be indicated for resectable pancreatic body/tail carcinomas situated near the root of the splenic artery. Our investigation regarding the relationship between radicality and the distance between the edge of the tumor and the splenic artery root in patients who underwent standard DP revealed that microscopically positive margins were detected more frequently in patients with tumors situated ≤10 mm from the splenic artery origin than in those with tumors >10 mm from the origin of the splenic artery [30]. Therefore, we suggest that DP-CAR should be performed to obtain an R0 resection in patients with potentially resectable pancreatic body/tail carcinomas with tumors located ≤10 mm from the splenic artery origin.

Our study also demonstrated that the overall survival rate of patients with no histopathologic evidence for invasion of either the portal venous system or artery (double-negative invasion) was greater than that of other patients. With regard to artery invasion, Kanda and colleagues [31] reported that invasion of the splenic artery is a crucial prognostic factor in patients with carcinoma of the body/tail of the pancreas. Moreover, extended pancreatectomy with major arterial resection did not result in long-term survival in previous reports [32–38]. Therefore, we carefully evaluated the patients with double-negative invasion into the portal venous system and the arterial system by preoperative imaging to determine indications for DP-CAR. However, the diagnostic accuracy of even the most sensitive modern imaging techniques is not equivalent to that of the microscope. Radiographic abutment of tumor and vessel does not necessarily indicate true vascular invasion.

The Role of the Appleby Operation and Arterial Resection

Recent studies have reported that arterial en bloc resection in patients undergoing pancreatectomy for pancreatic cancer is associated with poor short- and long-term outcomes. These studies indicate that arterial resection may yield overall survival durations comparable to those obtained with standard resection and better than those observed following palliative bypass [12, 33, 34]. However, arterial resection is associated with significantly higher morbidity and mortality rates, which limit the oncological benefit of operations in which it is used [32]. In general, we conclude that arterial en bloc resection may be justified in highly selected patients owing to the potential survival benefit compared to resection, but that these patients should be treated within the bounds of clinical trials and within the context of a multimodality strategy [32–34].

The ability of the modified Appleby operation to achieve wider surgical margins relative to a

standard DP is viewed as a potential benefit of the operation. In many borderline resectable cancers of the pancreatic head, the carcinoma abuts the superior mesenteric artery. This artery and the nerve plexus around it represent an absolute anatomic boundary of the surgical dissection. However, the modified Appleby procedure can extend the clearance of the surgical margin wider than it otherwise might be achieved using standard DP by enhancing the depth of dissection, behind the tumor by taking the aortic surface as a boundary. Another advantage of this procedure is the ability to relieve the cancer pain by celiac axis en bloc resection combined with removal of the tumor infiltrating plexuses. Recent studies have reported resolution rates of cancer pain after this procedure as high as 86–100 % [1, 12, 13] and improved quality of life after the procedure. The nutritional status and quality of life of the patients after this surgery were well maintained, and planned adjuvant therapy was generally received [39].

Preoperative Preparation for the Modified Appleby Operation (DP-CAR)

Several investigators have reported performing the modified Appleby operation without preoperative coil embolization of the CHA [13]. However, embolization has been suggested to decrease the risk of ischemia-related complications. The safety and efficacy of preoperative coil embolization still needs to be evaluated in clinical trials so its necessity remains controversial.

Preoperative coil embolization of the CHA requires collaboration between the surgeon and the interventional radiologist. The surgeons should precisely describe the planned ligation/division site, and the radiologist should place the coil appropriately to avoid coil migration into the arteries that are intended to be preserved [40, 41]. The diameter of the inferior pancreaticoduodenectomy is usually increased by about 1.5–2 times by the procedure.

Preparation of Instruments for the Modified Appleby Operation (DP-CAR)

The surgical instruments used in the modified Appleby operation (DP-CAR) are similar to those of ordinary pancreatic resection. The aortic clamps should be prepared in case of injury or a short ligation margin of the celiac trunk. Doppler ultrasonography should be performed routinely to evaluate intrahepatic arterial and portal flow.

The Procedure and Pitfalls of the Original Appleby Operation (DP-CAR)

The specific procedure we use for DP-CAR is as follows. First, the right gastroepiploic artery/vein and right gastric artery/vein are encircled by vessel tapes and preserved. Before the neck of the pancreas is transected, the bifurcation of the gastroduodenal artery (GDA) and the CHA is exposed, followed by exposure of the origin of the PHA. Confirmation that the periarterial nerve plexus around the bifurcation is negative for cancer cell infiltration should be performed using frozen samples to evaluate resectability in patients whose tumor is adjacent to this region. Kocher's maneuver should be performed in case of accidental bleeding from the portal venous system. The gastrocolic trunk is preserved for venous return from the stomach. Transection of the pancreas is performed at a site sufficient to resect a margin of normal tissue to reduce the likelihood for cancer cell infiltration. In a patient whose tumor involves the portal vein, the resection and reconstruction of the portal vein are performed antecedently. After pancreatic transection, the dissection of the retroperitoneum must be performed from the right to left side in the manner of a radical antegrade modular pancreatosplenectomy procedure because the surgical field will be better and safer for the surgeon and assistants in case of bleeding [42]. By en bloc dissection of the lymph nodes around the CHA, the right celiac

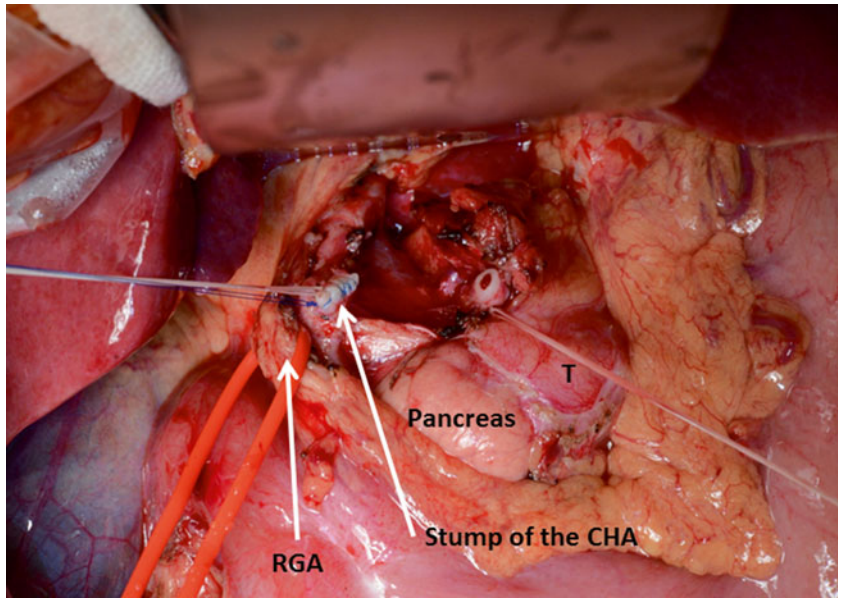

Fig. 16.3 The common hepatic artery was divided just proximal to the origin of the gastroduodenal artery. *T* pancreatic adenocarcinoma, *CHA* common hepatic artery, *RGA* right gastric artery

ganglion and celiac nerve plexus, as well as the origin of the celiac axis are exposed. Blood flow through the PHA, the right gastric artery, and the right gastroepiploic artery can then be confirmed by palpation; the intrahepatic arterial flow can also be checked by intraoperative Doppler ultrasonography after clamping the end of the CHA in patients who have undergone preoperative embolization of the CHA. The CHA is divided just proximal to the origin of the GDA (Fig. 16.3). In cases with dog-leg branching of the PHA and GDA, great care must be taken to preserve both arteries by avoiding ligation of bifurcation site (Figs. 16.4 and 16.5). By lifting the cut end of the distal pancreas and the CHA to the left, the superior mesenteric artery (SMA) can be dissected from the surrounding lymph nodes and nerve plexus toward its origin. Great care should be taken to preserve the inferior pancreaticoduodenal artery (IPDA) arising from the SMA or the first jejunal artery. The origin of the celiac axis is identified circumferentially just above the aorta and is divided. The origin and the direction of inferior phrenic arteries should be carefully noted in dissecting around the celiac axis in front of the aorta (Fig. 16.6).

Postoperative Complications After Modified Appleby Operation (DP-CAR)

The rates of morbidity following this procedure are high as shown in Table 16.2. The presence of postoperative hemorrhage from the resected stump of the CHA due to a pancreatic fistula after DP-CAR is difficult to rescue by interventional radiology techniques. Therefore, a novel procedure to reduce the risk of pancreatic fistula formation is urgently needed for DP-CAR, especially in patients with thick pancreatic parenchyma [43, 44].

DP-CAR may also be associated with gastric or hepatic ischemia. In several institutions, total gastrectomy is added if severe ischemia of the stomach is observed during the operation and if the surgeon cannot exclude the possibility of future necrosis of the remnant stomach. Unplanned arterial reconstruction is required in patients with accidental injury [1]. The sequelae of ischemic gastropathy include irregular, shallow, and wide ulcerations in the cardia of the stomach and/or symptoms of delayed gastric

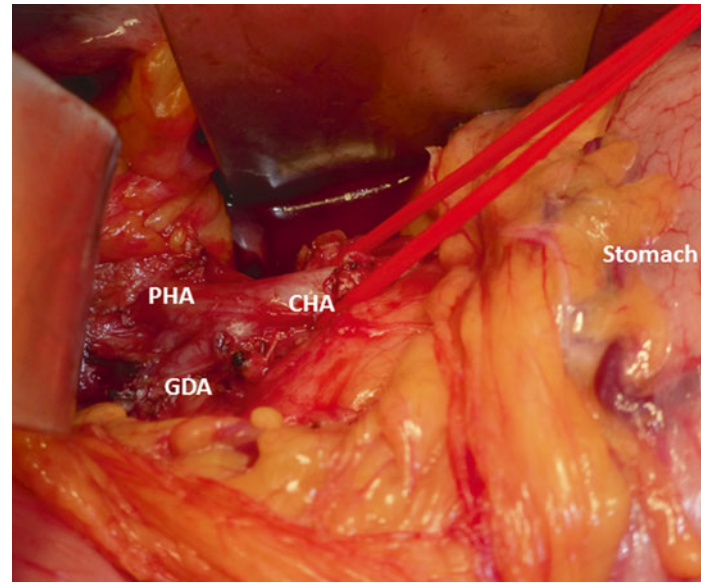

Fig. 16.4 In cases with "dog-leg" branching of proper hepatic artery and gastroduodenal artery, great care must be taken to preserve both arteries by avoiding ligation of the bifurcation site. *CHA* common hepatic artery, *PHA* proper hepatic artery, *GDA* gastroduodenal artery

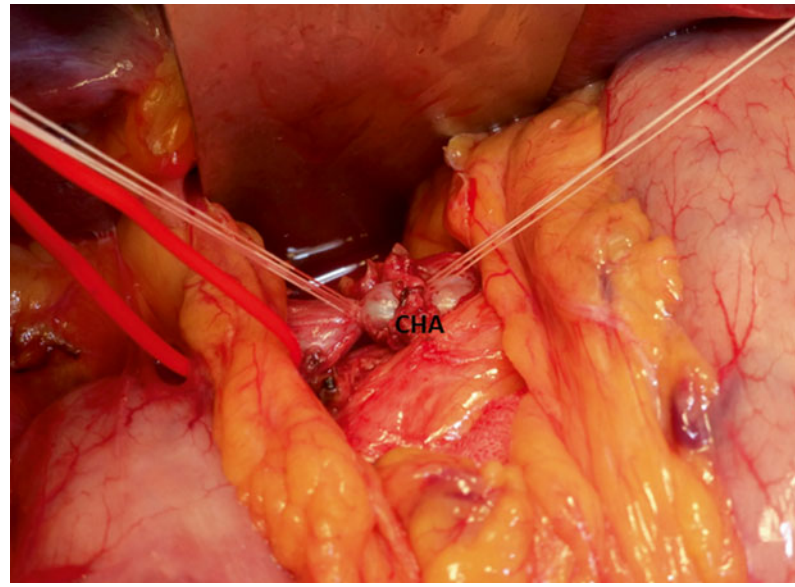

Fig. 16.5 The common hepatic artery was ligated in the distal side. Pulsation within the proper hepatic artery and gastroduodenal artery was confirmed again after ligation. CHA, common hepatic artery

emptying; gastropathy may directly effect postoperative recovery and the schedule for adjuvant chemotherapy. With regard to hepatic ischemia, recent studies have reported a low incidence of clinically relevant hepatic infarction, and abnormal liver function usually resolves after several days. Necrotic cholecystitis due to spasms of the GDA and/or PHA has been reported. Although there is no clear evidence that preoperative embolization of the CHA reduces risks of ischemia, preoperative angiography should be performed to elucidate the arterial anatomy.

The greatest concern following the removal of the plexus around the celiac axis and the superior

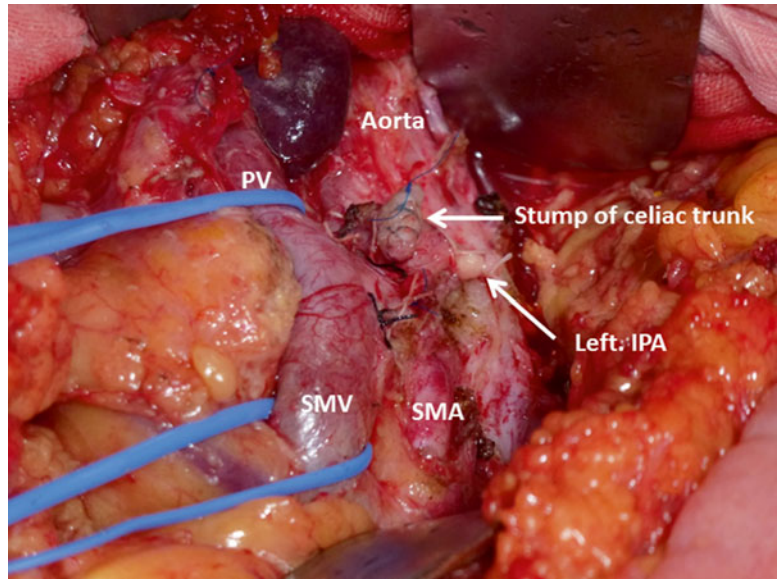

Fig. 16.6 The origin and the direction of inferior phrenic arteries should be carefully noted while dissecting around the celiac axis in front of the aorta. *PV* portal vein, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery, *IPA* inferior phrenic artery

mesenteric artery is diarrhea, because it can influence nutritional status and quality of life. In many studies, diarrhea can be controlled by medication well enough to maintain quality of life and nutritional status, usually with loperamide hydrochloride and rarely with tincture of opium [1].

Feasibility and Safety Compared to Standard Distal Pancreatectomy

The mean operative time associated with DP-CAR is significantly longer than that associated with standard DP due to the extended dissection and radical dissection required in the former; however, no differences with regard to mean estimated blood loss or mean postoperative hospital stay between the two procedures have been identified. In terms of postoperative complications, previous studies have reported the incidence of postoperative pancreatic fistula [45] and revealed no significant differences between the modified Appleby operation and standard distal pancreatectomy; however, delayed gastric emptying (DGE) was more common in the modified Appleby operation. Otherwise, mortality has been reported to be low in the recent literature [46] (Table 16.2).

Preservation of the LGA

Despite the favorable surgical outcomes described recently, DGE or ischemic gastropathy after the modified Appleby operation (DP-CAR) remains a common and frustrating complication. The incidence of DGE induced by ischemic gastropathy ranges from 13.0 and 30.8 % in published series [1, 14]. It is not a life-threatening complication, but it may result in a prolonged hospital stay and leads to a decreased quality of life, poor nutritional status, and delayed administration of postoperative adjuvant chemotherapy. In a recent study, several patients underwent combined total gastrectomy to prevent gastric ischemic complications during the modified Appleby operation (DP-CAR) [1, 14].

The LGA develops as the first branch of the celiac trunk embryologically, and it may branch antecedently in 68–72 % of cases as described above [25, 26]. The procedures used for the modified Appleby operation (DP-CAR) routinely include en bloc resection of the LGA [1], although cancer of the pancreas body requiring DP-CAR may not involve the LGA or the nerve plexus that surrounds it. We therefore attempt to preserve the LGA in patients whose LGA branches anteced-

Table 16.2 Postoperative complications after DP-CAR

Author (Reference)	Reported year	Number of cases (*n*)	MST[a] (month)	1-year survival rate (%)[a]	Ischemia-related complication (%)[b]	Morbidity (%)	Mortality (*n*)
Hishinuma, et al. [11]	2007	7	19	30	0	29	0
Hirano et al. [1]	2007	23	21	42	13[c]	48	0
Wu et al. [12]	2010	11	14	9	0[c]	36	1
Takahashi et al. [13]	2011	16	10	35	0[c]	56	1
Yamamoto et al. [14]	2012	13	21	25	38[c]	92	0
Okada et al. [30]	2013	16	25	42	6	44	0

[a]Data include estimated survival time/rates
[b]Ischemia-related complications in the stomach, duodenum, and liver
[c]Preventive combined resection of the total stomach was performed

ently and in whom the distance between the LGA and carcinoma is more than 10 mm.

To clarify whether LGA preservation in DP-CAR (modified DP-CAR) could reduce the incidence of DGE and other postoperative complications, the medical records of 37 consecutive patients who underwent DP-CAR were evaluated for the incidence of DGE [47]. 23 patients (62 %) had LGA-resecting DP-CAR (conventional DP-CAR) and 14 patients (38 %) underwent distal pancreatectomy with resection of the CHA and splenic artery, with preservation of the LGA (modified DP-CAR) for pancreatic carcinoma. The patients with tumors situated more than 10 mm away from the antecedent branching LGA underwent modified DP-CAR (Fig. 16.7a–c). The antecedent branching of the LGA was found in 19 patients (51 %) in this study. In the conventional DP-CAR group, the LGA was involved in 20 patients (87.0 %). Clinically relevant DGE rates were 30 % in the conventional DP-CAR group, and 0 % in the modified DP-CAR group ($p=0.035$). The R0 rate was higher in the modified DP-CAR group (79 %) compared to the conventional DP-CAR group (43 %) ($p=0.048$). Univariate and multivariate analyses demonstrated that resection of the LGA was an independent risk factor for increased incidence of DGE (Table 16.3). Therefore, modified DP-CAR significantly reduced the incidence of DGE in comparison to conventional DP-CAR [47].

In this series, the blood supply and innervation associated with the distal stomach, including right gastric and right gastroepiploic arteries, and antral nerve branch, were all preserved, but the proximal stomach blood supply including the left gastroepiploic and short gastric arteries was resected in all cases. A recent study reported resection of LGA-induced ischemia of the proximal remnant stomach during distal pancreatectomy, demonstrating only circulation of blood from the esophagogastric junction through the intramural capillary network by intraoperative indocyanine green fluorescence angiography [48]. In addition, we have anecdotally observed, using computed tomography or angiography, the right gastric and right gastroepiploic arteries slowly developing to supply the proximal stomach following DP-CAR in several cases. It should be noted that the right gastric and right gastroepiploic veins were preserved, and the left gastric and short gastric veins were resected in all cases, so the degree of venous congestion of the stomach following DP-CAR should have been similar between the two groups in this study. We have concluded based upon all of these observations that gastric ischemia apparently leads to DGE after DP-CAR, and that the LGA should be preserved if it is anatomically and oncologically possible so as to reduce the likelihood of ischemic gastropathy after DP-CAR. In patients whose collateral flow has been injured or has

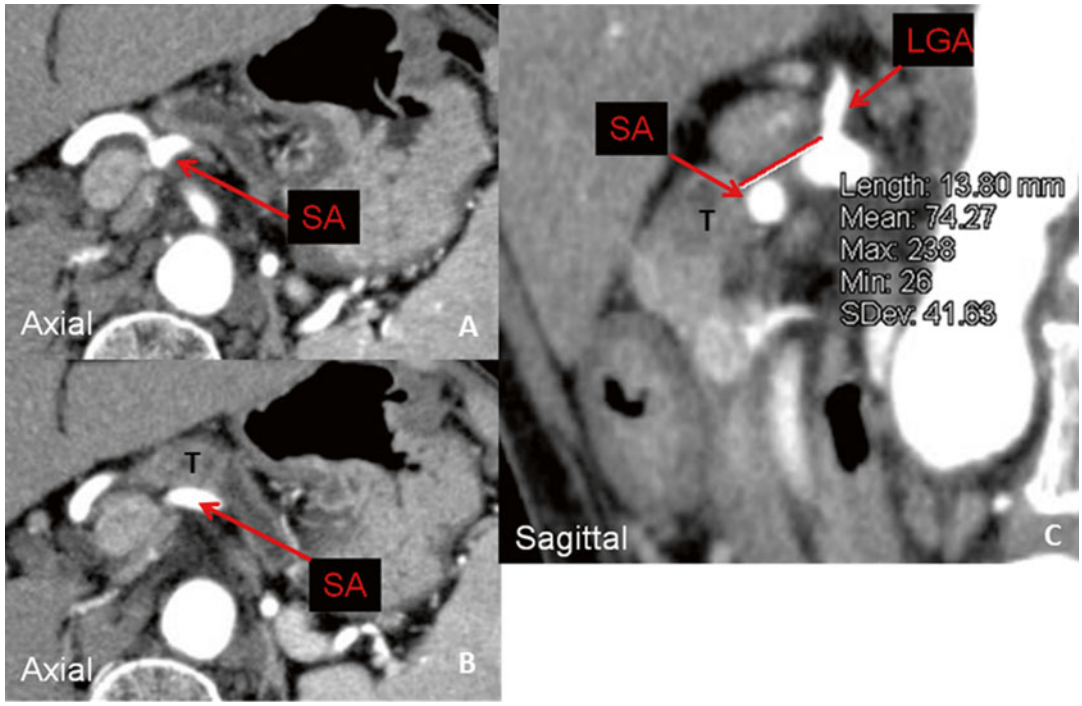

Fig. 16.7 Patients with tumors situated more than 10 mm away from the antecedent branching left gastric artery undergo distal pancreatectomy with resection of the common hepatic artery and splenic artery, with preservation of the left gastric artery (modified DP-CAR) at our institution. (**a**) An axial image shows the root of the splenic artery. (**b**) An axial image reveals tumor abutment of the splenic artery. (**c**) A sagittal image shows that the distance between the tumor and the left gastric artery was 13.8 mm in this case. *SA* splenic artery, *LGA* left gastric artery

Table 16.3 Univariate and multivariate analyses: risk factors of delayed gastric emptying in patients who underwent DP-CAR

	Univariate analysis			Multivariate analysis		
Factor	DGE(−) ($n=23$)	DGE(+) ($n=14$)	p-Value	OR	95 % CI	p-Value
Tumor size >4 cm	9	8	0.328			
NAC(R)T	8	7	0.493			
LGA resection	10	13	0.004	10.071	1.035–98.011	0.047
Portal vein resection	3	5	0.215			
Operative time >360 min	8	9	0.101			
EBL > 700 mL	8	9	0.101			
Residual tumor (R1)	6	10	0.015	3.702	0.666–20.579	0.135
Pancreatic fistula (Grade B, C)	2	6	0.035	3.975	0.456	0.211
Ischemic gastroduodenal complication	0	2	0.137			

DGE delayed gastric emptying, *OR* odds ratio, *NAC(R)T* neoadjuvant chemo (radiation) therapy, *LGA* left gastric artery, *EBL* estimated blood loss

been identified as insufficient during surgery, arterial reconstruction by saphenous vein or middle colic artery–gastroepiploic artery bypass should be considered [49].

Surgical Technique Preserving LGA

When the intent is to preserve LGA, the right gastroepiploic artery/vein and the right gastric artery/vein are encircled by vessel tape and preserved, and cancer cell infiltration into the periarterial nerve plexuses around GDA or CHA is ruled out as soon as possible to evaluate resectability. Additionally, the pulsation of GDA and PHA is checked before clamping. After clamping the CHA, the pulsation is reconfirmed, and the CHA is then ligated and divided at the distal part described as above (Fig. 16.3). The LGA is encircled by vessel tape to preserve it during the early phase of surgery. By lifting the distal pancreas and the CHA by en bloc dissection of the lymph nodes with arteries around the CHA, the origin of the celiac axis is exposed, and the celiac axis is encircled (Fig. 16.8). After confirming by intraoperative frozen section (Fig. 16.9) that a patient is negative for cancer cell infiltration into the nerve plexus surrounding the LGA, the celiac artery is divided just after the branching of the LGA (Fig. 16.10). The resection and reconstruction of the portal vein is performed before the radical antegrade modular pancreatosplenectomy procedure. The depth of the dissecting layer of the retroperitoneum is controlled with a wide margin according to the tumor position. Figure 16.11 shows the surgical field after modified DP-CAR.

Survivals After Modified Appleby Operation (DP-CAR)

A few long-term survivors have been reported in a small number of previous studies. Table 16.2 shows the survival after this procedure as reported in the recent literature. The (estimated) median survival time was 9–42 months. Several investigators have reported better survival in patients

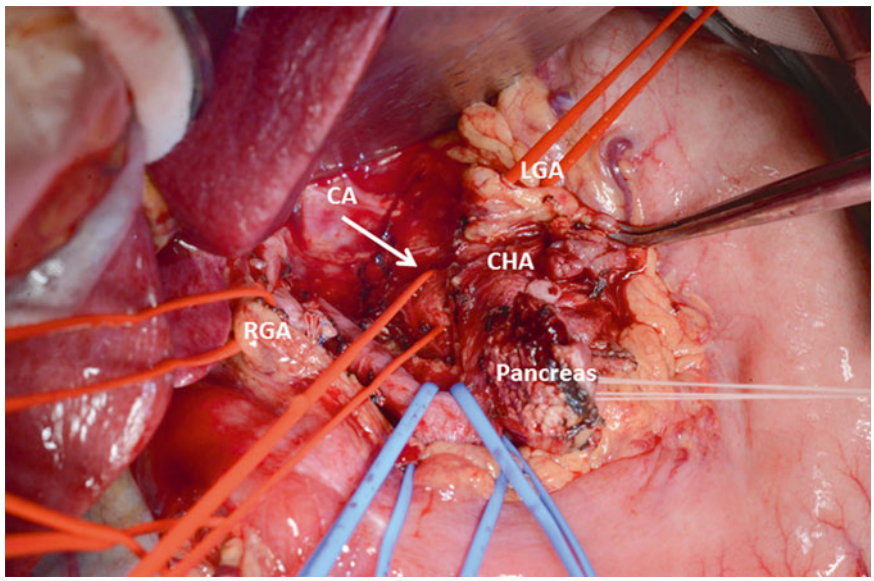

Fig. 16.8 With the distal pancreas and the common hepatic artery lifted by en bloc dissecting of lymph nodes with arteries, the origin of the celiac axis was exposed (*circled*). *CA* celiac axis, *RGA* right gastric artery, *CHA* common hepatic artery, *LGA* left gastric artery

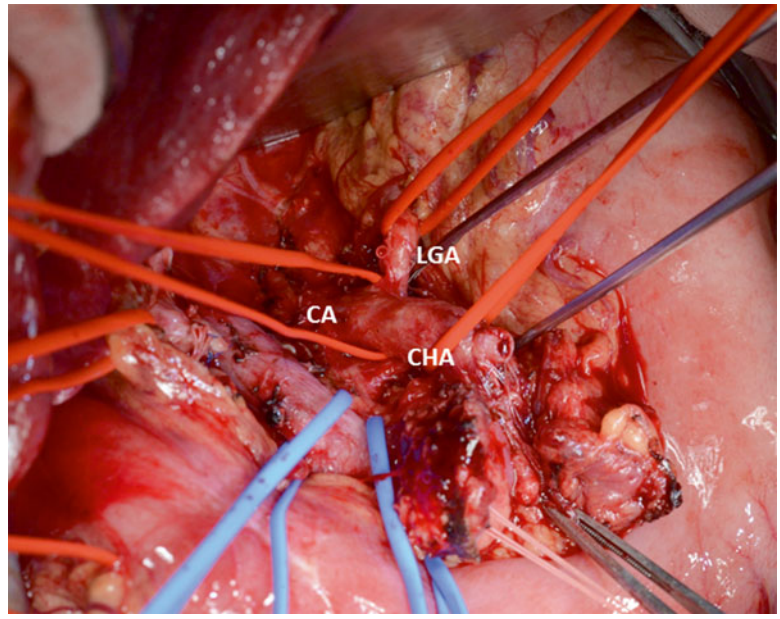

Fig. 16.9 Several frozen sections confirmed by intraoperative histopathological examination that the patients were negative for cancer cell infiltration of the nerve plexus surrounding the left gastric artery. *CA* celiac axis, *CHA* common hepatic artery, *LGA* left gastric artery

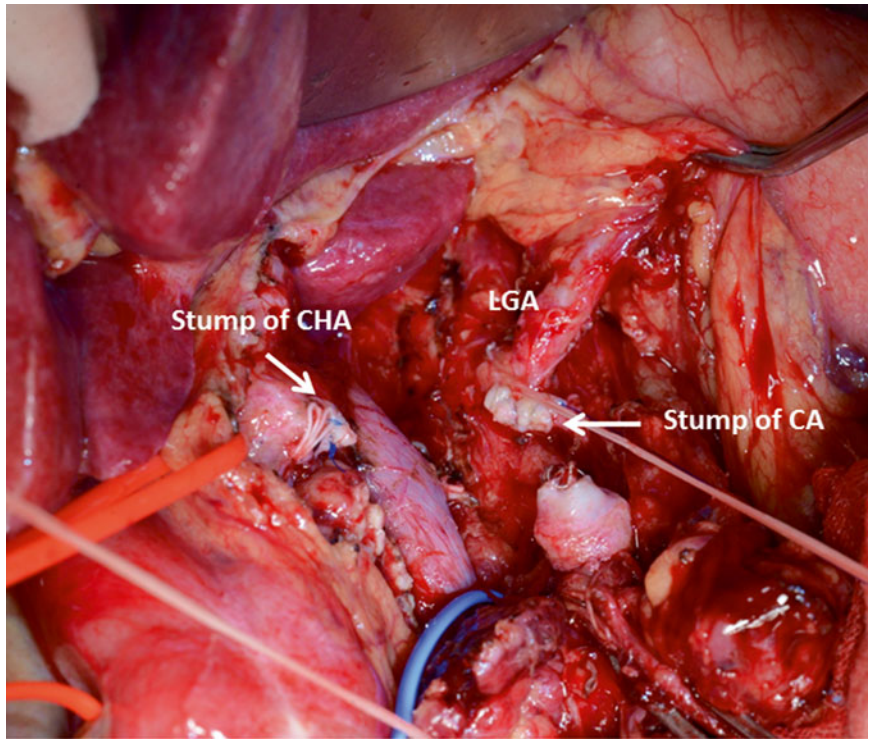

Fig. 16.10 The celiac artery was divided just after the branching of the left gastric artery. *CA* celiac axis, *RGA* right gastric artery, *CHA* common hepatic artery, *LGA* left gastric artery

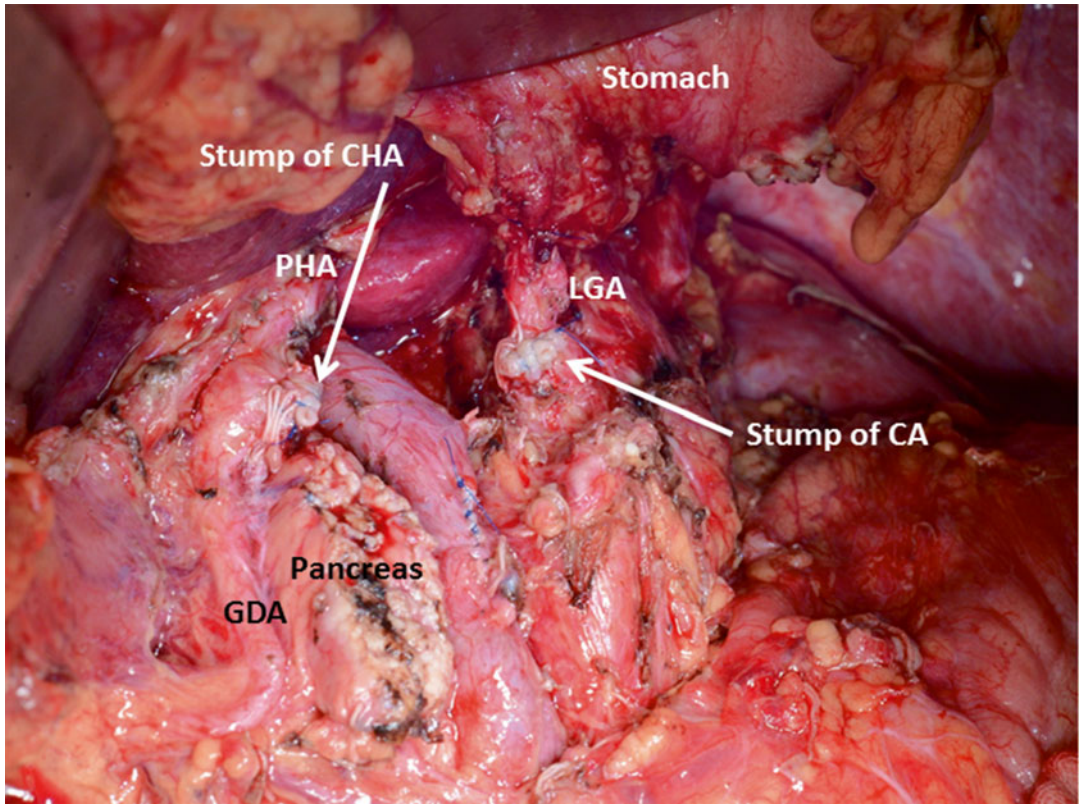

Fig. 16.11 The surgical field after modified DP-CAR. *CA* celiac axis, *RGA* right gastric artery, *CHA* common hepatic artery, *LGA* left gastric artery, *PHA* proper hepatic artery, *GDA* gastroduodenal artery

who underwent modified Appleby operation compared to those with R2/M1 resection. In our series, there were no differences in survival between patients who underwent standard DP and DP-CAR between 2005 and 2010; 52 consecutive patients underwent distal pancreatectomy with D2 node dissection, including 36 standard DP and 16 DP-CAR, for pancreatic body/tail carcinoma [30].

The Modified Appleby Operation as Adjuvant Surgery

Adjuvant surgery for patients with initially unresectable pancreatic cancer has a major role to play due to improvements in chemotherapy [50]. Chemotherapy sometimes initially shrinks a pancreatic body/tail carcinoma abutting the celiac axis and aorta enough to be resected by surgery. Satoi et al. [50] reported ten cases (17 %) of modified Appleby operation (DP-CAR) as adjuvant surgery in 58 initially unresectable pancreatic cancer patients, including 41 with locally advanced cancer and 17 with metastatic cancer, who underwent adjuvant surgery with a favorable response to nonsurgical anticancer treatments over 6 months and concluded that adjuvant surgery for initially unresectable pancreatic cancer patients including modified Appleby operation can be a safe and effective treatment. Recent stronger regimens of chemotherapy may be all the more effective in downstaging cancer cases and providing a surgical option for patients with initially unresectable pancreatic cancer [51–53].

Specimen of Modified Appleby Operation

In our study, histopathologic examination revealed positive margins for tumor infiltration in 10 patients (63 %) [30]. Microscopically positive margins, except for the pancreatic margin, were frequently identified in two dissected sites. The surface in front of the aorta at the root of the celiac axis in the periarterial nerve plexuses was involved in four patients. The retropancreatic tissue around the periarterial nerve plexuses of the celiac artery was involved in six patients. These positive margins were situated at the posterior extent of the resected specimens (Figs. 16.12 and 16.13) [54]. Great care should be taken in assessing these hot spots histopathologically. These sites may also represent targets of non-surgical anticancer treatment in cases of locally advanced/borderline resectable pancreatic cancer.

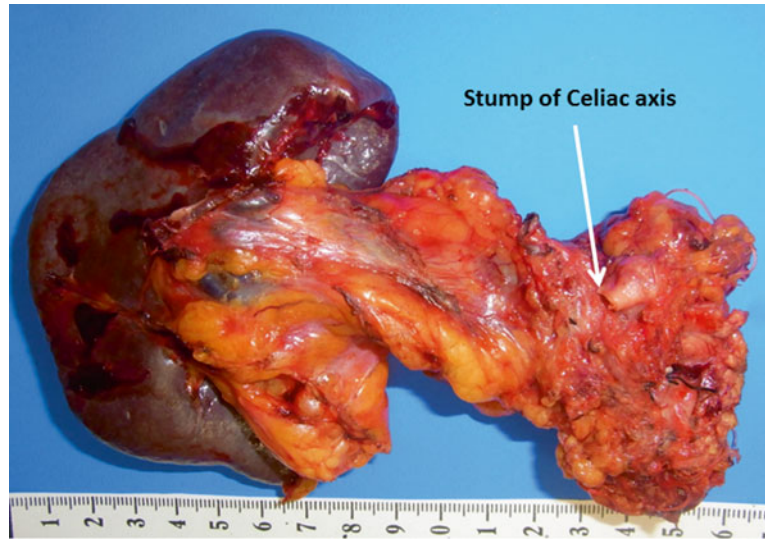

Fig. 16.12 The posterior side of the resected specimen from a modified DP-CAR. The bifurcations of the splenic artery and common hepatic artery are not visible at the dissection surface

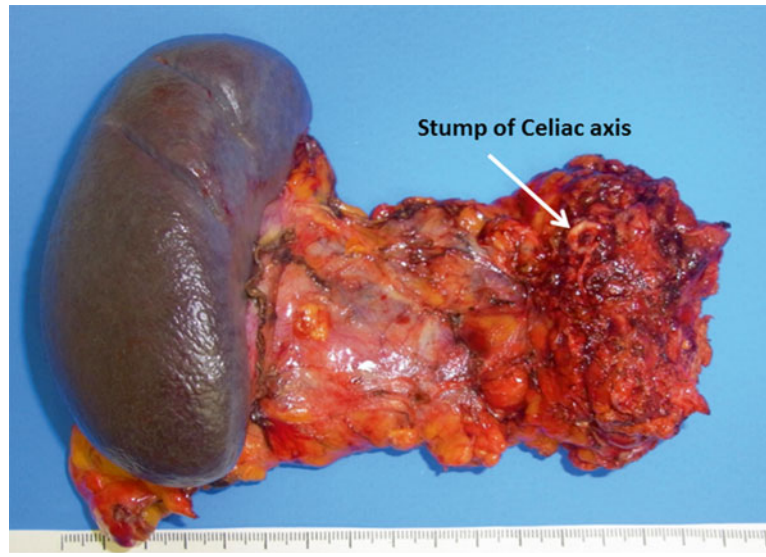

Fig. 16.13 The posterior side of the resected specimen from a modified Appleby operation (DP-CAR)

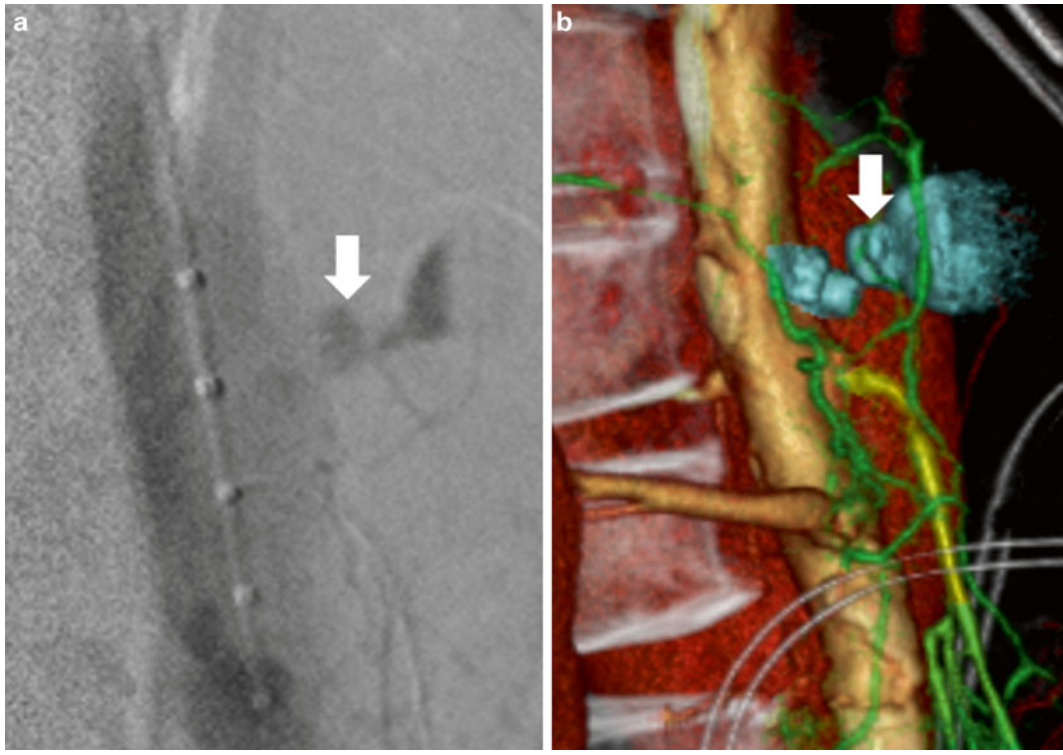

Fig. 16.14 A sagittal image of angiography (**a**) and three-dimensional computed tomography (**b**) show the extravasation (*arrows*) from a pseudoaneurysm in the celiac trunk

The presence or absence of arterial wall invasion must also be precisely investigated. Arterial abutment or encasement identified on preoperative imaging studies should be confirmed by histopathological examination.

How to manage the postpancreatectomy hemorrhage from the stump of celiac axis. In cases with prolonged pancreatic fistula after the modified Appleby operation, the worst complication may be bleeding from a pseudoaneurysm of the celiac trunk (Fig. 16.14) [55, 56]. Immediate interventional radiology consultation is recommended in such cases. An aortic stent covering the origin of the celiac artery may rescue some cases (Fig. 16.15). Close collaboration between surgeons and interventional radiologists is clearly essential in the management of patients at high risk for hemorrhage.

Conclusions

The modified Appleby operation (DP-CAR) is feasible and safe compared with standard DP. The procedure may be justified in highly selected patients owing to its potential survival benefit relative to non-operative therapies. Patients undergoing DP-CAR should be treated with multimodality therapy. A recent modification of the modified Appleby operation (i.e., modified DP-CAR) with preservation of the LGA may be preferable.

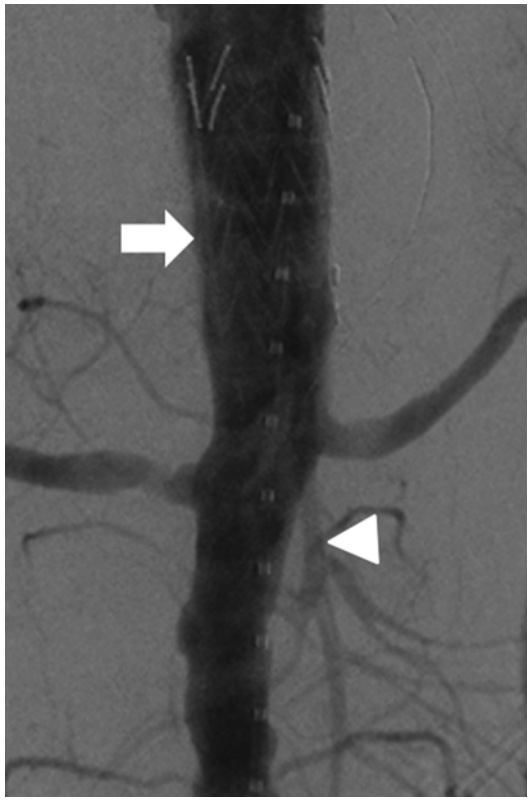

Fig. 16.15 The extravasation disappeared just after the aortic stent (*arrow*) was expanded. Patency of the superior mesenteric artery was preserved (*arrowhead*)

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Surgery for Borderline Resectable Pancreatic Cancer: The Japanese Experience

17

Shuji Isaji, Masashi Kishiwada, and Hiroyuki Kato

Introduction

For patients with pancreatic ductal adenocarcinoma (PDAC), surgical resection is the only potentially curative therapy, and R0 resection is a strong prognostic indicator for long-term survival. The National Comprehensive Cancer Network (NCCN) has developed guidelines to define tumor resectability in PDAC, in order to improve patient selection for surgery and to identify the likelihood of an R0 resection. Using NCCN criteria, PDAC tumors are classified as resectable (R), borderline resectable (BR), locally unresectable (LUR), or metastatic. Borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) tumors are those associated with a significant likelihood of an incomplete resection when surgery is used as primary therapy. On the contrary, locally unresectable pancreatic ductal adenocarcinoma (LUR-PDAC) are locally advanced tumors, such as those which encase the superior mesenteric artery (SMA) or celiac artery (CA) greater than 180° of those vessels' circumferences, or those associated with unreconstructable portal vein (PV)/superior mesenteric vein (SMV) occlusion. Chemotherapy and Chemoradiotherapy (CRT) before surgery for BR- or LUR-PDAC may provide for the early treatment of micrometastatic disease, allow for the identification of patients with metastatic disease prior to surgery, and increase the R0 resection rate, resulting in a reduced risk for local tumor recurrence and improvement in outcome. In this chapter, we provide the outcomes of surgery for BR- and LUR-PDAC using data both from a multi-institutional survey administered in Japan and from our institution, paying special attention to the role of CRT before surgery and innovations in surgical technique for BR-PDAC.

Borderline Resectable Pancreatic Ductal Adenocarcinoma

Multi-Institutional Survey in Japan

After the first description of marginally resectable adenocarcinoma of the pancreas which was defined as tumor involvement of the PV, SMV, or a major artery by Mehta et al. [1] in 2001, the NCCN adopted the term "borderline resectable" in 2006 and this definition has been subsequently modified [2]. The NCCN published a more precise description of BR-PDAC in 2009 [3], and we promptly collected and analyzed clinical data from 624 patients with BR-PDAC tumors of the pancreatic head or body as defined by the 2009

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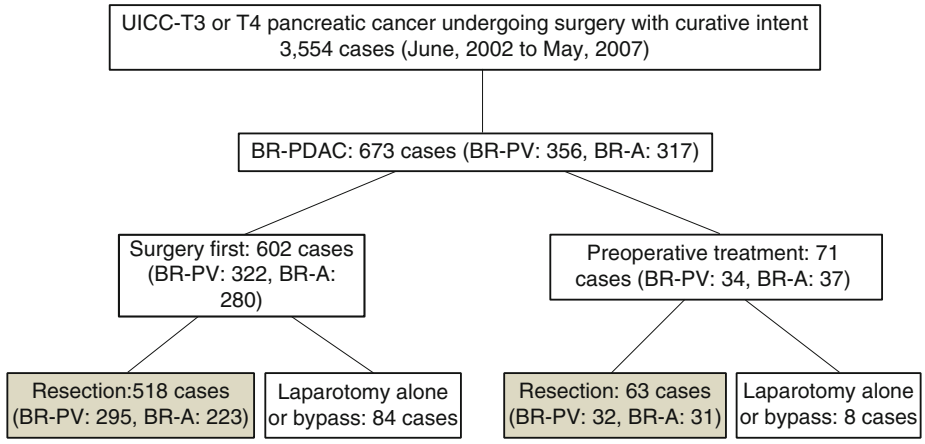

Fig. 17.1 Flow diagram of patients with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC) obtained from questionnaires administered to attendees of the 37th annual meeting of the Japanese Society of Pancreatic Surgery (JSPS) in 2010. Patients had radiographic findings suggestive of vascular involvement limited to the PV (portal vein) alone (BR-PV), or to the HA (hepatic artery), SMA (superior mesenteric artery) and/or CA (celiac artery) with or without PV (BR-A)

NCCN guidelines. These data were acquired by distributing questionnaires to member institutions of the Japanese Society of Pancreatic Surgery (JSPS) at the 37th JSPS Annual Meeting in 2010, at a time when the optimal treatment of patients with BR-PDAC was unclear because of a lack of well-designed studies [4]. On the basis of these data, we found that BR-PDAC tumors could be divided into two distinct subgroups: tumors with PV/SMV invasion alone and tumors with major arterial invasion. We found that patient survival was highly dependent upon this BR-PDAC substage.

At the time of writing this chapter, we reanalyzed the entire database of 673 patients with BR-PDAC (which included patients with BR-PDAC tumors of the pancreatic tail that were not included in the prior analysis) that was created at the 37th JSPS Annual Meeting in 2010. We focused on two distinct categories of tumors according to the degree of vascular invasion which was suggested by imaging findings on triphasic contrast-enhanced multi-detector computed tomography: BR-PV (apparent vascular invasion limited to the PV alone) and BR-A (apparent involvement of the HA, SMA, and/or CA). Among the 673 patients with BR-PDAC of the pancreatic head, body, or tail, there were 356 patients with BR-PV tumors and 317 with BR-A tumors. Surgery was performed as primary therapy in 602 patients and preoperative treatment was administered to 71 patients prior to surgery (Fig. 17.1). The preoperative regimens used for these 71 patients were: radiotherapy + gemcitabine (Gem) ($n=31$), Gem alone ($n=20$), Gem + 5-fluorouracil (5-FU) ($n=11$), radiotherapy alone ($n=4$), Gem + S1 ($n=2$), radiotherapy + Gem + 5-FU ($n=1$), radiotherapy + oral fluorinated pyrimidine derivative (S-1) ($n=1$), and 5-FU alone ($n=1$). The clinical profile of the 673 patients with BR-PDAC is shown in Table 17.1. In this series, resection of major vessels was aggressively performed at pancreatectomy: PV/SMV resection was performed in 441 (65.5 %) cases, SMA resection was performed in 24 (3.6 %) cases, CA resection was performed in 58 (8.6 %) cases, HA resection was performed in 60 (8.9 %) cases, and IVC resection was performed in 14 (2.1 %) cases.

The 3- and 5-year survival rates of all 673 patients were 15.9 % and 9.7 %, respectively (Fig. 17.2a). Survival curves plotted for patient groups according to the radiographic extent of vascular involvement (Fig. 17.2b) demonstrated that the 3- and 5-year survival rates were significantly higher in BR-PV patients than in BR-A

Table 17.1 Background of the 673 cases with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC)

	BR-PDAC ($n=673$)
Age (years old)	63.8 ± 7.9
Gender (male/female)	388/285
Performance status (0-1/2/3/4)	655/16/2/0
Elevation of CA19-9 (yes/no)	502/171
Elevation of CEA (yes/no)	237/436
Tumor location (Ph-Pb/Pt)	624/49
Tumor diameter (mm)	36.1 ± 10.1
T factor (T3/T4)	508/165
N factor (N0/N1)	341/332
Preoperative stage (2a/2b/3/4)	268/222/156/27
Preoperative histological/cytological evidence (yes/no)	100/573
Surgical procedure (PD/DP/TP/bypass/lap/others)	450/105/26/62/28/2
PV/SMV resection (yes/no)	441/232
SMA resection (yes/no)	24/649
CA resection (yes/no)	58/615
HA resection (yes/no)	60/613
IVC resection (yes/no)	14/659
Radicality (R0/R1/R2)	377/148/148
POPF (yes/no)	60/613
Hospital death (yes/no)	29/644

Ph pancreatic head, *Pb* pancreatic body, *Pt* pancreatic tail, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *lap* laparotomy, *PV/SMV* portal vein/superior mesenteric vein, *CA* celiac artery, *HA* hepatic artery, *IVC* inferior vena cava, *POPF* postoperative pancreatic fistula

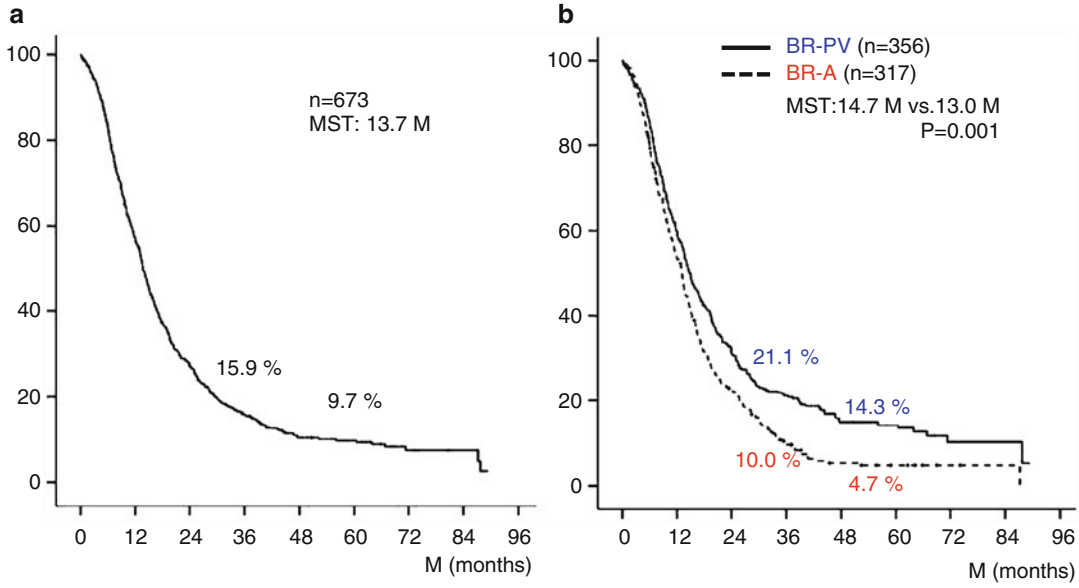

Fig. 17.2 (**a**) Kaplan–Meier survival curve of 673 patients with borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC). The 3- and 5-year survival rates in total 673 patients were 15.9 % and 9.7 %, respectively. (**b**) Kaplan–Meier survival curves plotted for patient groups according to radiographic findings. Patients had radiographic findings suggestive of vascular involvement limited to the PV (portal vein) alone (BR-PV), or to the HA (hepatic artery), SMA (superior mesenteric artery) and/or CA (celiac artery) with or without PV (BR-A). The 3- and 5-year survival rates of BR-PV cases ($n=356$) were significantly better than those of BR-A cases ($n=317$): 21.1 % and 14.3 % vs. 10.0 % and 4.7 %, respectively ($p=0.001$). *MST* median survival time

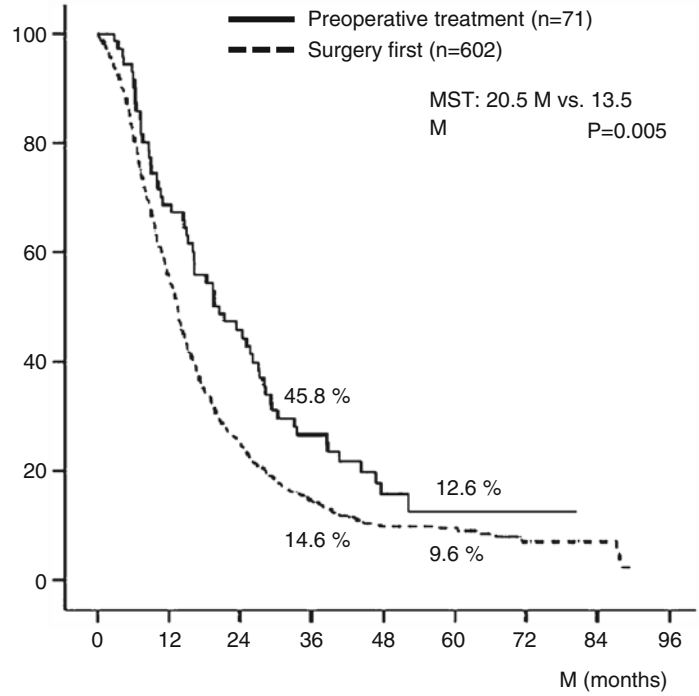

Fig. 17.3 Kaplan–Meier survival curves of BR-PDAC patients stratified by receipt of preoperative treatment. The 3- and 5-year survival rates of patients who received preoperative chemotherapy and/or radiotherapy ($n=71$) were significantly better than those who did not ($n=602$): 45.8 % and 12.6 % vs. 14.6 % and 9.6 %, respectively ($p=0.005$). Details of the 71 patients who received preoperative treatment were as follows: radiotherapy+gemcitabine (Gem) ($n=31$), Gem alone ($n=20$), Gem+5-fluorouracil (5-FU) ($n=11$), radiotherapy alone ($n=4$), Gem+S1 ($n=2$), radiotherapy+Gem+5-FU ($n=1$), radiotherapy+oral fluorinated pyrimidine derivative (S-1) ($n=1$), and 5-FU alone ($n=1$). *BR-PDAC* borderline resectable pancreatic adenocarcinoma, *MST* median survival time

patients: 21.1 % and 14.3 % vs. 10.0 % and 4.7 %, respectively ($p=0.001$). Furthermore, patients who received preoperative treatment ($n=71$) had 3- and 5-year survival rates significantly higher than those of patients who underwent surgery first ($n=602$): 45.8 % and 12.6 % vs. 14.6 % and 9.6 %, respectively ($p=0.005$) (Fig. 17.3). Survival curves according to the type of vascular invasion were also compared between surgery first and preoperative treatment groups (Fig. 17.4). Among patients who underwent surgery first, the 3- and 5-year survival rates were significantly higher in patients with BR-PV tumors ($n=322$) than in those with BR-A tumors ($n=280$): 19.0 % and 12.2 % vs. 9.4 % and 4.1 %, respectively ($p=0.001$). In the preoperative treatment group, the 3- and 5-year survival rates of patients with BR-PV tumors ($n=34$) were higher (though not significantly so) than those of patients with BR-A ($n=37$) tumors: 40.4 % and 19.2 % vs. 13.9 % and 8.4 %, respectively ($p=0.061$).

We also compared survival curves and the status of residual tumor (R) between these radiographic subtypes among the patients who received operations with curative intent. In the surgery first group (Fig. 17.5a), the 3- and 5-year survival rates of patients with BR-PV tumors ($n=295$) were significantly higher than those of patients with BR-A tumors ($n=223$): 19.9 % and 15.2 % vs. 11.5 % and 5.0 %, respectively ($p=0.004$). Moreover, patients with BR-PV tumors had a significantly higher R0 resection rate as compared to patients with BR-A tumors: 73.2 % vs. 52.0 % ($p<0.001$). Among patients who received preoperative therapy (Fig. 17.5b), the 3- and 5-year survival rates were higher (though not significantly so) in BR-PV

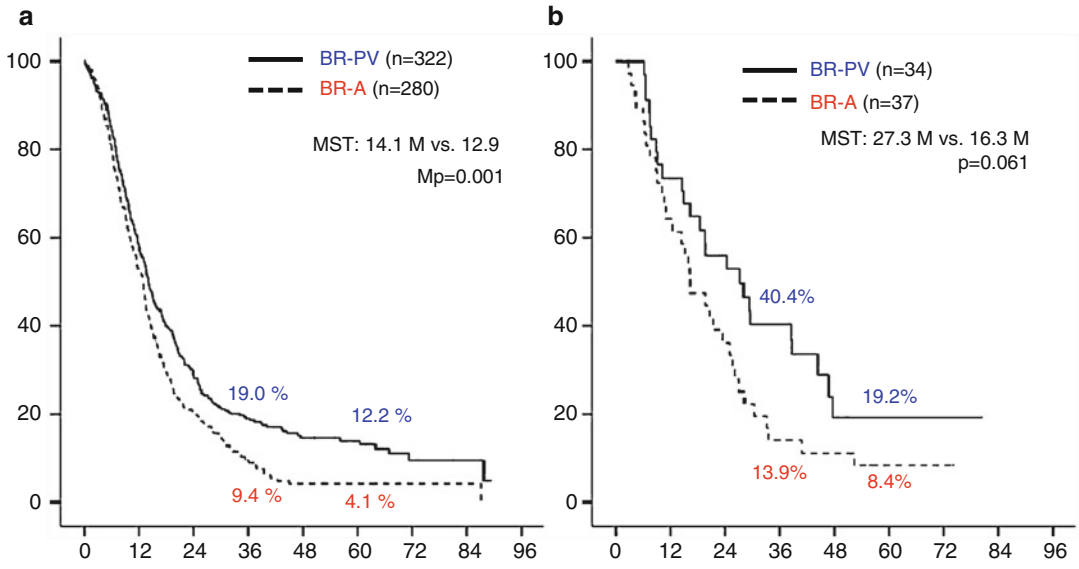

Fig. 17.4 (**a**) Kaplan–Meier survival curves according to borderline resectable subtype (BR-PV or BR-A) in BR-PDAC patients who underwent surgery first ($n=602$). The 3- and 5-year survival rates of BR-PV cases ($n=322$) were significantly better than those of BR-A patients ($n=280$): 19.0 % and 12.2 % vs. 9.4 % and 4.1 %, respectively ($p=0.001$). (**b**) Kaplan–Meier actuarial overall survival curves according to the extent of radiographic vascular involvement in the patients treated preoperatively. The 3- and 5-year survival rates of BR-PV patients ($n=34$) were better than those of BR-A cases ($n=37$): 40.4 % and 19.2 % vs. 13.9 % and 8.4 %, respectively ($p=0.061$). *BR-PDAC* borderline resectable pancreatic adenocarcinoma, *MST* median survival time, *BR-PV* BR-PDAC with portal vein invasion alone, *BR-A* BR-PDAC with major artery involvement

($n=32$) patients than in BR-A ($n=31$) patients: 42.9 % and 20.4 % vs. 16.7 % and 10.0 %, respectively ($p=0.092$). R0 resection rates did not significantly differ between BR-PV and BR-A subgroups: 75.0 % vs. 64.5 %.

In our previous study evaluating 624 patients with BR-PDAC tumors of the pancreatic head and body [4], multivariate analysis revealed four independent prognostic factors: surgical resection, major artery involvement as determined using triphasic contrast-enhanced multi-detector computed tomography, the administration of preoperative treatment, and the administration of postoperative chemotherapy. In the 539 patients who underwent resection, we also identified two independent prognostic factors: major artery involvement and the status of residual tumor. Furthermore, we revealed that the R0 resection rate of patients with tumors that appeared to involve the major arteries was significantly lower than that of patients with tumors that did not appear to involve the major arteries on preoperative imaging. The results of our subsequent reevaluation of the entire database of 673 patients with BR-PDAC tumors of the head, body, or tail of the pancreas showed that the R0 resection rate of patients who underwent surgery first was significantly lower among patients with BR-A tumors than patients with BR-PV tumors. However, the R0 resection rate of patients who received preoperative therapy did not significantly differ between patients who had BR-PV and BR-A tumors. Although the number of patients with BR-PDAC who received preoperative treatment in these analyses was small, these data suggests that preoperative treatment with CRT may enhance the rate of R0 resection, which in turn may improve therapeutic outcomes.

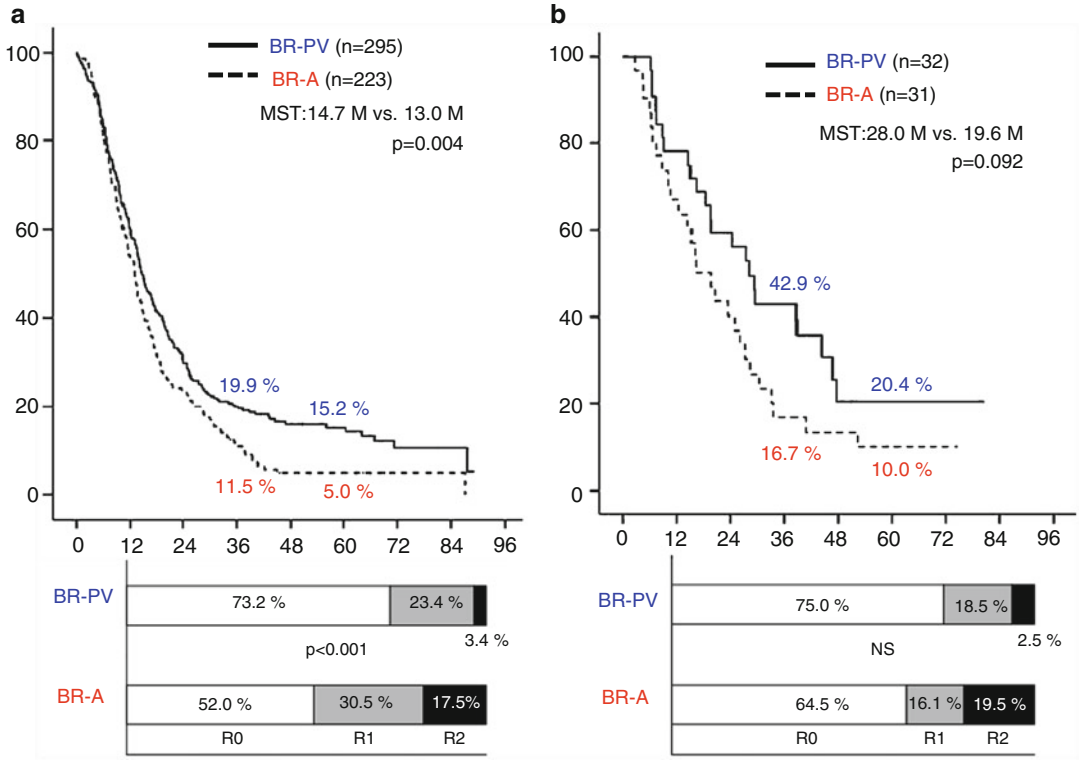

Fig. 17.5 (**a**) Kaplan–Meier survival curves and the status of residual tumor (R) according to the borderline resectable subtype (BR-PV or BR-A) in the patients who underwent surgery first whose tumor was resected ($n=518$). The 3- and 5-year survival rates of BR-PV cases ($n=295$) were significantly better than those of BR-A patients ($n=223$): 19.9 % and 15.2 % vs. 11.5 % and 5.0 %, respectively ($p=0.004$). Moreover, BR-A patients showed significantly lower rates of R0 resection as compared to BR-PV patients. (**b**) Kaplan–Meier survival curves and the status of residual tumor according to the borderline subtype in the patients who underwent resection following preoperative treatments. The 3- and 5-year survival rates of BR-PV cases ($n=32$) were better than those of BR-A cases ($n=31$): 42.9 % and 20.4 % vs. 16.7 % and 10.0 %, respectively ($p=0.092$). R0 resection rates did not differ between BR-PV and BR-A. *BR-PDAC* borderline resectable pancreatic adenocarcinoma, *MST* median survival time, *BR-PV* BR-PDAC with portal vein invasion alone, *BR-A* BR-PDAC with major artery involvement

Preoperative Chemoradiotherapy at Our Institution

In an attempt to increase the R0 resection rate of patients with locally advanced PDAC, our institution has used preoperative gemcitabine-based chemoradiation therapy (GEM-CRT) since February 2005 [5–7]. Although the benefits of preoperative CRT in this clinical scenario have been suggested by others [8–10], the extent to which histopathologic response to CRT is associated with survival in this setting has historically been unclear. We therefore explored the relationship between histopathologic response (as determined by evaluation of UICC-T3 and T4 PDAC tumors resected following GEM-CRT) and prognosis and found that in T3 tumors, histological response was a significant prognostic indicator, whereas in T4 tumors, GEM-CRT did not lead to a beneficial histological response [5]. Furthermore, we examined the relationship between the intratumoral expression of human equilibrative nucleoside transporter (hENT1, the main GEM transporter into cells) in the resected specimens and the outcome of GEM-CRT in patients with T3 and T4 PDAC [6]. We showed that the hENT1 expression in PDAC cells was strongly associated with the outcome of preoperative GEM-CRT treatment,

suggesting that this biomarker might represent a useful predictor of the effect of gemcitabine-based therapies. From these studies, we concluded that GEM-CRT, even when used for patients with advanced PDAC, allowed for the identification of candidates for aggressive resection at the time of reassessment, facilitated an increase in the R0 resection rate, and improved the prognosis of patients with positive hENT1 expression [7].

Our treatment protocol for preoperative GEM-CRT was used to treat 124 PDAC patients from February 2005 to October 2011, and thereafter we switched our protocol to S-1/GEM-based CRT (S-1/GEM-CRT) which was used to treat 96 patients from November 2011 to September 2014 (Fig. 17.6). Although we initially referred to our protocol as neoadjuvant or preoperative CRT [5, 6], we subsequently adopted the term "CRT followed by surgery (CRT-S)" because approximately half of the patients registered in the protocol were staged as having unresectable PDAC—for these patients, the term "preoperative treatment" was not appropriate [7]. S-1 is an oral agent that contains tegafur, gimeracil, and oteracil [11], and the agent appears at least equivalent to or even more active than 5-FU when combined with radiotherapy for locally advanced PDAC [12, 13]. Recently, a randomized phase III study of GEM plus S-1, S-1 alone, or GEM alone in patients with locally advanced and metastatic PDAC (GEST Study) showed that monotherapy with S-1 demonstrated noninferiority to GEM in overall survival with good tolerability and that GEM plus S-1 significantly improved progression-free survival as compared with GEM [14].

The surgical outcomes of all 220 patients enrolled in our CRT-S protocol are shown in Table 17.2. Staged using NCCN criteria [3], there were 18 patients (8.2 %) with resectable tumors, 106 (48.2 %) with borderline resectable tumors and 96 (43.6 %) with unresectable tumors.

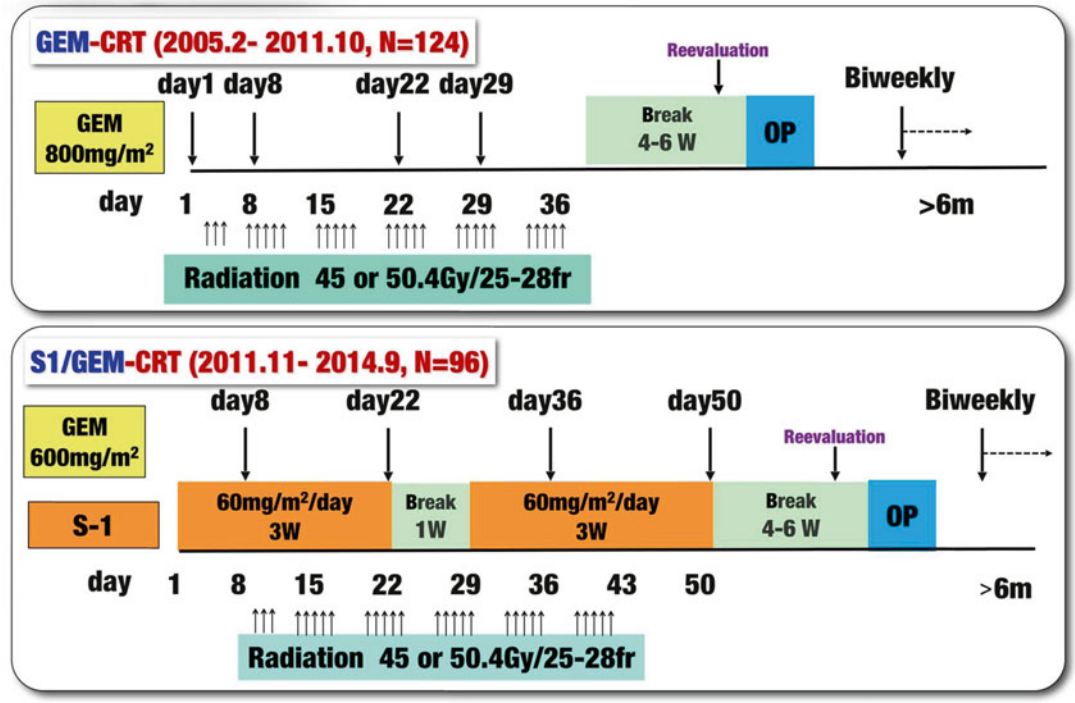

Fig. 17.6 Treatment protocol of chemoradiotherapy (CRT) followed by surgery (CRT-S) at Mie University Hospital. Gemcitabine-based CRT (GEM-CRT) had been performed in 124 patients from February 2005 to October 2011, and S-1/GEM-based CRT (S-1/GEM-CRT) had been performed in 96 patients from November 2011 to September 2014. *Gy* gray, *fr* fraction, *W* week

Table 17.2 Surgical outcomes of patients enrolled for the chemoradiotherapy followed by surgery (CRT-S) protocol at Mie University Hospital, 2005.2- 2014.9 ($n=220$)

	R ($n=18$)	BR ($n=106$)	LUR ($n=96$)
Resection rate	61.1 % (11/18[a])	76.4 % (81/106[b])	44.8 % (43/96[c])
Surgical procedure (PD/DP/TP)	5/6/0	74/6/1	28/15/0
Major vessels resection	PV: 3 (27.3 %)	PV: 73 (90.1 %)	PV: 38 (88.4 %)
		CHA: 3	CA: 9, CHA: 3
		I VC: 1	
R0	100 % (11/11)	86.4 % (70/81)	58.1 % (25/43)
R1	0 % (0/11)	11.1 % (9/81)	34.9 % (15/43)
R2	0 % (0/11)	2.5 % (2/81)	7.0 % (3/43)

R resectable, *BR* borderline resectable, *LUR* locally unresectable, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *PV* portal vein, *CHA* common hepatic artery, *IVC* inferior vena cava, *CA*: celiac artery
[a,b,c:] including 3 (a), 5 (b), and 1 (b) patients who did not return to hospital

The resection rate was significantly lower in patients with unresectable tumors (44.8 %) as compared to those with BR tumors (76.4 %). Combined resection of PV was aggressively performed in BR and in LUR: 90.1 % and 88.4 %, respectively. The R0 resection rate was also significantly lower in LUR (58.1 %) as compared to R (100 %) and BR (86.4 %). Survival curves according to the three resectability groups (R, BR, and LUR) in the total 220 patients and in the 135 patients who underwent curative-intent resection after CRT are shown in Figs. 17.7 and 17.8, respectively. Survival was significantly different among the three resectability groups: 5-year survival rates of 41.0 % (R), 24.2 % (BR), and 4.4 % (LUR) were observed in all treated patients, and 5-year survival rates of 68.6 % (R), 29.3 % (BR), and 9.5 % (LUR) were observed among patients who underwent resection.

CA19-9 has been accepted as a measure of PDAC burden; however, the role of CA19-9 in the evaluation of patients with preoperative CRT prior to planned surgical resection has not been well evaluated. Previously, we explored whether serum CA19-9 levels could be used as an index of response to GEM-CRT, especially in BR-PDAC patients [7]. By comparing the level of pre-CA19-9 with that measured at the time of reassessment (post-CA19-9), the reduction rate was calculated as follows: (pre-CA19-9–post-CA19-9)/(pre-CA19-9) (%). When the reduction rate was greater than 50 % regardless of the pre-CA19-9 level, GEM-CRT was defined as being effective. Survival curves for the 43 BR-PDAC patients were analyzed according to the CA19-9 reduction rate. The 3-year survival rate was significantly higher in 23 patients who had a CA19-9 reduction rate of 50 % or more than in 20 patients who had a CA19-9 reduction rate less than 50 % (36.6 % vs. 7.9 %, $P=0.0003$). In the present cohort study using 102 BR-PDAC patients in whom serum levels of CA19-9 could be reassessed after GEM-CRT or S1/GEM-CRT, the 3-year survival rate was significantly higher in 60 patients who had a CA19-9 reduction rate of 50 % or more than in 42 patients who had a CA19-9 reduction rate less than 50 % (37.0 % vs. 21.0 %, $P=0.011$) (Fig. 17.9). As compared to the previous study, the 3-year survival rate in patients who had a CA19-9 reduction rate less than 50 % improved from 7.9 % to 21.0 %, while in patients with a CA19-9 reduction rate of 50 % or more, it did not change (36.6 % vs. 37.0 %).

As previously mentioned, multi-institutional data analysis on the 673 patients with BR-PDAC in Japan according to the type of vascular invasion (BR-PV or BR-A) revealed that BR-PV patients had significantly better survival than BR-A patients, presumably because BR-A patients had a lower rate of R0 resection. In the present cohort study using 102 BR-PDAC patients who could be reassessed after GEM-CRT or S1/GEM-CRT, the 3- and 5-year survival rates of BR-PV patients ($n=53$) were similar to

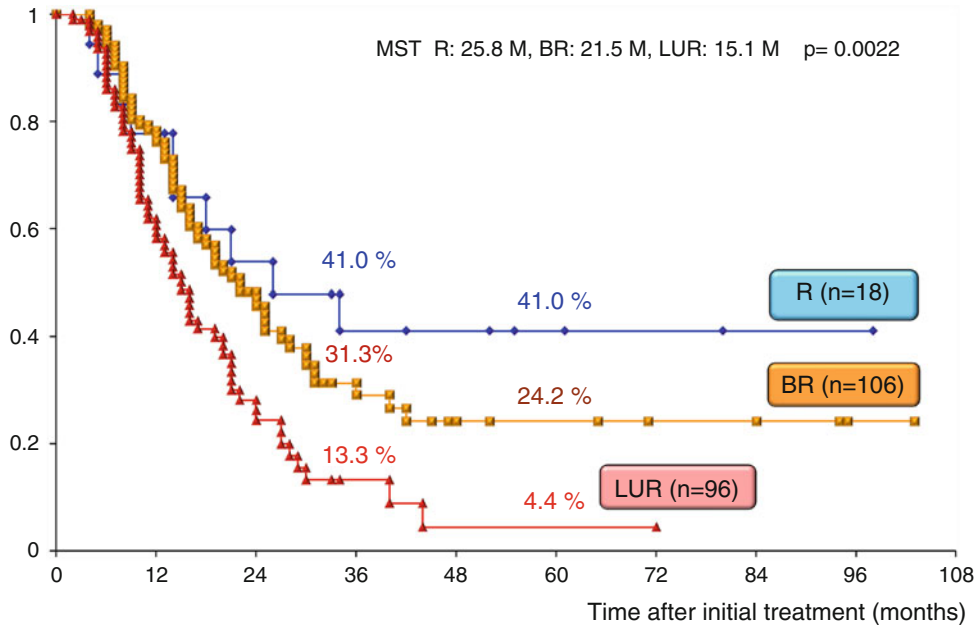

Fig. 17.7 Kaplan–Meier survival curves according to the three resectability groups (R, BR, and LUR) in the enrolled 220 patients who underwent chemoradiotherapy followed by surgery (CRT-S) at Mie University Hospital. *R* resectable, *BR* borderline resectable, *LUR* locally unresectable, *MST* median survival time

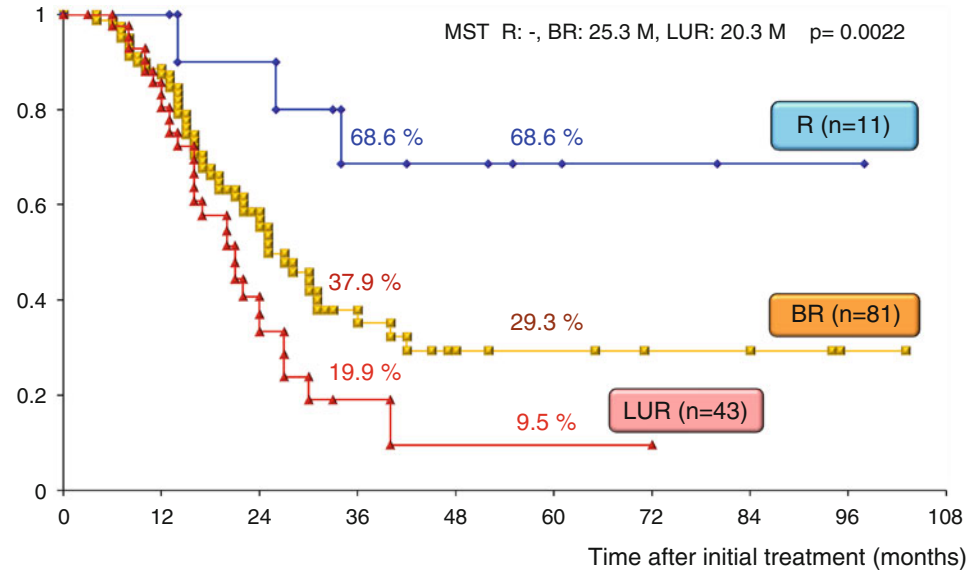

Fig. 17.8 Kaplan–Meier survival curves according to the three resectability groups (R, BR, and LUR) in the 135 patients who underwent curative-intent resection after CRT at Mie University Hospital. *R* resectable, *BR* borderline resectable, *LUR* locally unresectable. *MST* median survival time

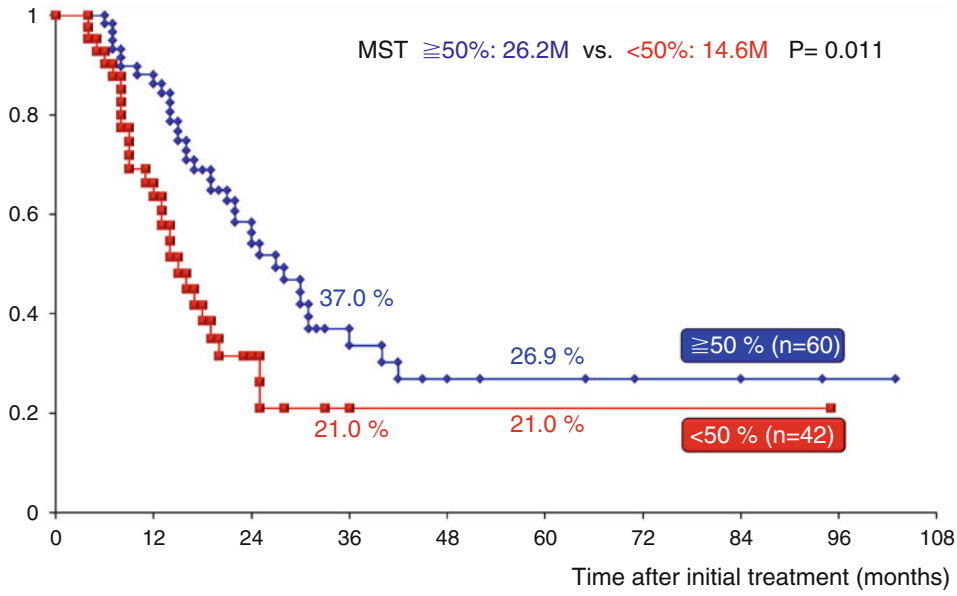

Fig. 17.9 Kaplan–Meier survival curves according to the CA19-9 reduction rate in BR-PDAC patients ($n=102$) in whom serum levels of CA19-9 could be reassessed after chemoradiotherapy at Mie University Hospital. We compared the level of pre-CA19-9 measured just before the initiation of treatment with that measured at the time of reassessment (post-CA19-9). The reduction rate was calculated as follows: (pre-CA19-9–post-CA19-9)/(pre-CA19-9) (%). *MST* median survival time

those of BR-A patients ($n=53$): 30.2 % and 23.5 % vs. 33.1 % and 24.9 %, respectively (Fig. 17.10a). Among 81 BR-PDAC patients who underwent curative-intent resection after CRT, the 3- and 5-year survival rates of BR-PV patients ($n=44$) were similar to those of BR-A patients ($n=37$): 35.3 % and 27.4 % vs. 41.7 % and 31.2 %, respectively (Fig. 17.10b). The R0 resection rate was significantly higher in BR-PV patients than in BR-A patients (97.7 % vs. 73.0 %, $P=0.001$). The R0 resection rates of BR-PV and BR-A patients were much higher in our institutional analysis as compared to those in the multi-institutional data analysis: 73.2 % and 52.0 %, respectively, in the patients who underwent surgery first and 75.0 % and 64.5 %, respectively, in those who underwent resection following preoperative therapy (Fig. 17.5). These data suggest that GEM-CRT and S1/GEM-CRT improve survival of patients with BR-PDAC, and especially of patients with BR-A disease, by enhancing the R0 resection rate.

Innovation of Surgical Technique for BR-PDAC After CRT

The Japan Pancreas Society's staging system of pancreatic cancer [15] named the connective tissue between the SMA/CA and the pancreatic head parenchyma, which contains not only the nerve plexus but also lymphatic, nervous, and vascular structures, as the PLph-I (the structures between the pancreatic head and the lateral side of SMA) and PLph-II (between the pancreatic head and the lateral side of CA). According to an interesting prior study of patients with PDAC who underwent pancreaticoduodenectomy (PD) with concomitant resection of SMA [16], it was found that the lymphatics and the nerve plexus around the SMA were frequently involved by cancer. PLph-I and -II, recently recognized by others as comprising the mesopancreas [17], were shown to be the primary sites of residual disease leading to a microscopically positive resection in patients with cancers of the pancre-

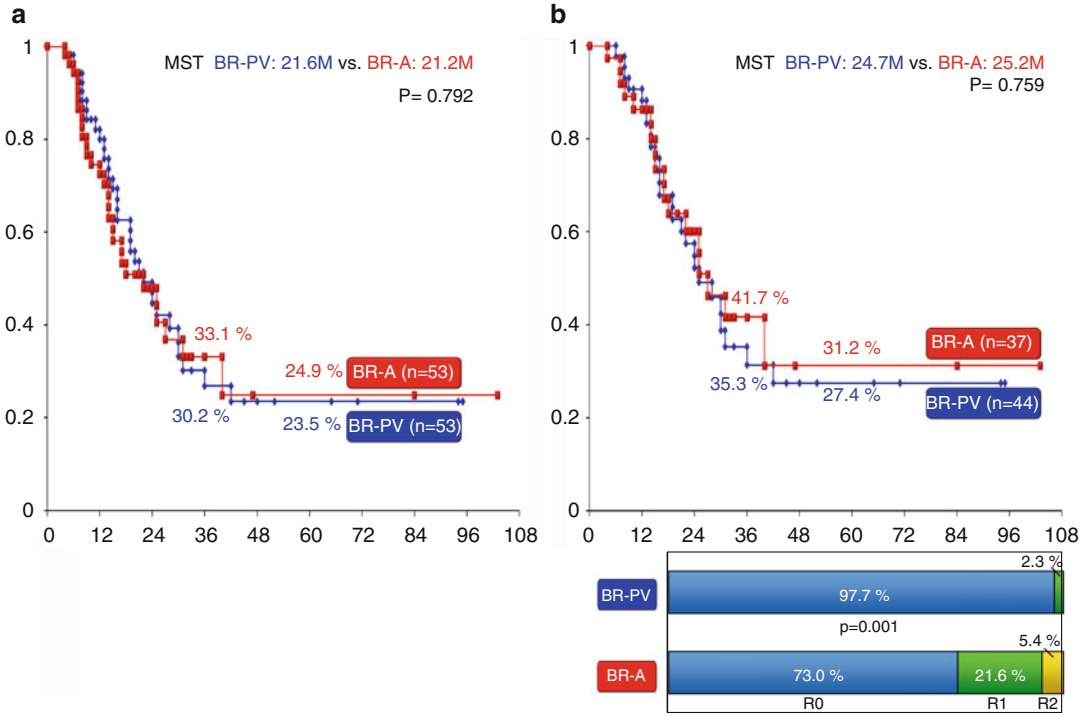

Fig. 17.10 (**a**) Kaplan–Meier survival curves according to the borderline resectable subtype (BR-PV or BR-A) in BR-PDAC patients ($n=106$) who underwent CRT-S. The 3- and 5-year survival rates of BR-PV cases ($n=53$) were similar to those of BR-A cases ($n=53$): 30.2 % and 23.5 % vs. 33.1 % and 24.9 %, respectively. (**b**) Kaplan–Meier actuarial overall survival curves according to the borderline resectable subtype (BR-PV or BR-A) in BR-PDAC patients ($n=81$) who underwent resection after CRT. The 3- and 5-year survival rates of BR-PV cases ($n=44$) were similar to those of BR-A cases ($n=37$): 35.3 % and 27.4 % vs. 41.7 % and 31.2 %, respectively. R0 resection rate was significantly higher in BR-PV than in BR-A. *BR-PDAC* borderline resectable pancreatic adenocarcinoma, *MST* median survival time, *BR-PV* BR-PDAC with portal vein invasion alone, *BR-A* BR-PDAC with major artery involvement, *CRT-S* chemoradiotherapy followed by surgery, *CRT* chemoradiotherapy

atic head, suggesting that complete resection of the mesopancreas might improve prognosis. Indeed, we hypothesized that PD with en bloc resection of the nerve plexus surrounding the SMA enhances R0 resection rate, especially for patients with BR-PDAC. In 2010, we developed the nerve plexus hanging maneuver using an anterior approach to the SMA for BR-PDAC of the pancreatic head following CRT and reported the outcomes of 21 patients treated with this approach [18].

Figure 17.11 shows a typical example of the anterior approach to the SMA using our nerve plexus hanging maneuver, in which a complete dissection of PLph-II on the lateral side of the SMA is performed. Tape is passed behind the nerve plexus between the pancreatic head and the lateral side of SMA ventral to the inferior vena cava (Fig. 17.11a), and another tape is passed in a space behind the nerve plexus (PLph-I) between the pancreatic head parenchyma and the root of the common hepatic artery (CHA).

CT images of a 60-year-old male with BR-A before and after S1/GEM-CRT are depicted in Fig. 17.12. Prior to the administration of CRT, the tumor (T) abutted the SMA over nearly 180° of its circumference (Fig. 17.12a). Following CRT, repeat cross-sectional imaging demonstrated a minimal radiographic response (Fig. 17.12b), but the serum level of CA19-9 had fallen from 128 to 23 U/m. In this case, the anterior wall of SMA toward its root was exposed and

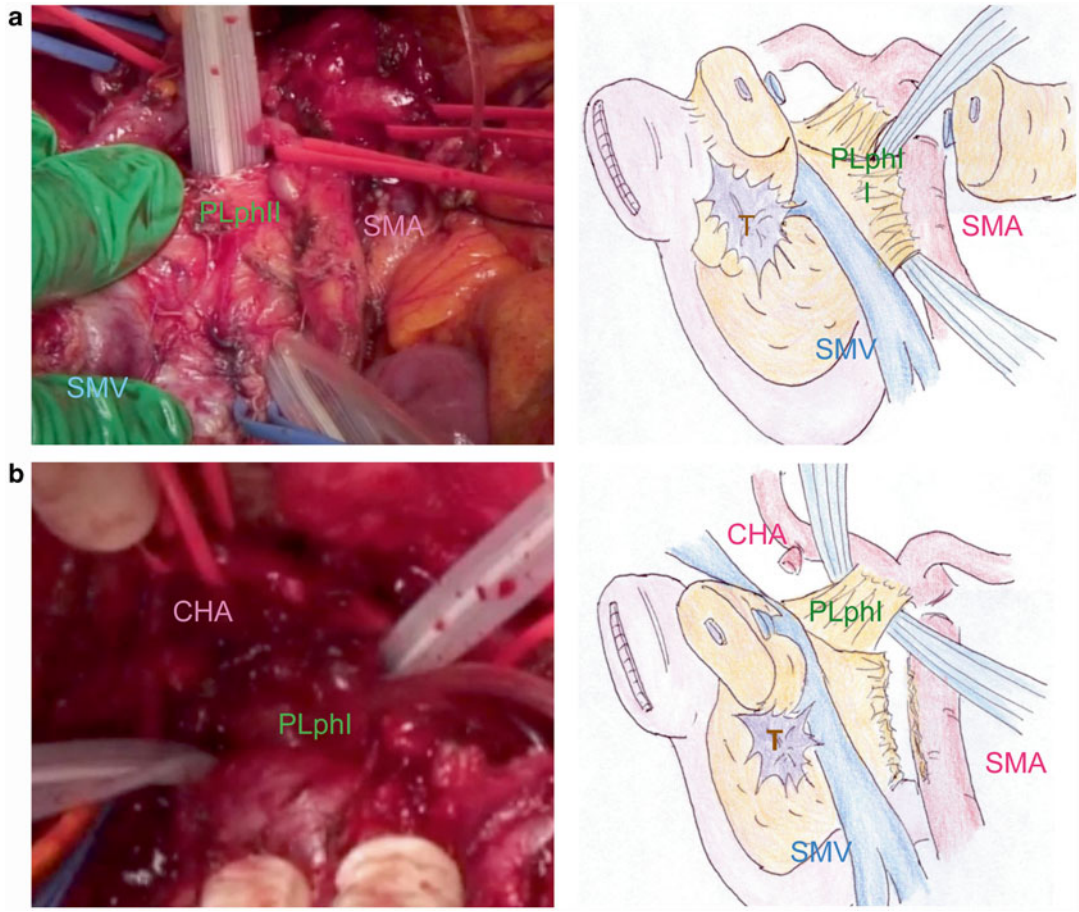

Fig. 17.11 Anterior approach to the SMA using nerve plexus hanging maneuver. (**a**) Dissection of the extra pancreatic nerve plexus II (PLph-II) on the lateral side of the SMA. A tape is passed behind the nerve plexus between the pancreatic head and the lateral side of SMA ventral to the inferior vena cava. (**b**) Dissection of the nerve plexus on the lateral side of the common hepatic artery (CHA) (PLph-I). Another tape is passed in a space behind the nerve plexus between the pancreatic head parenchyma and the root of the CHA. PLph-II: the nerve plexus between the pancreatic head and the lateral side of SMA, PLph-I: the nerve plexus between the pancreatic head parenchyma and the root of the CHA according to the Japan Pancreas Society staging system of pancreatic cancer

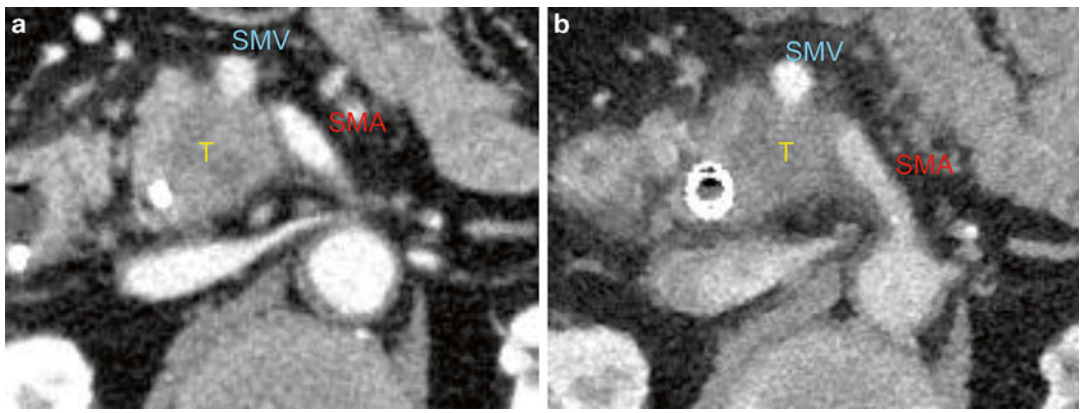

Fig. 17.12 CT images of a 60-year-old male with BR-A before and after S1/GEM-CRT. (**a**) Before CRT, tumor (T) abutted the superior mesenteric artery (SMA) nearly 180°. (**b**) After CRT with TS-1/gemcitabine and 50.4 Gy radiation, the tumor showed a minimal radiographic response, although CA19-9 levels decreased from 128 to 23 U/m. *BR-A* borderline resectable tumor with major artery involvement, *CRT* chemoradiotherapy

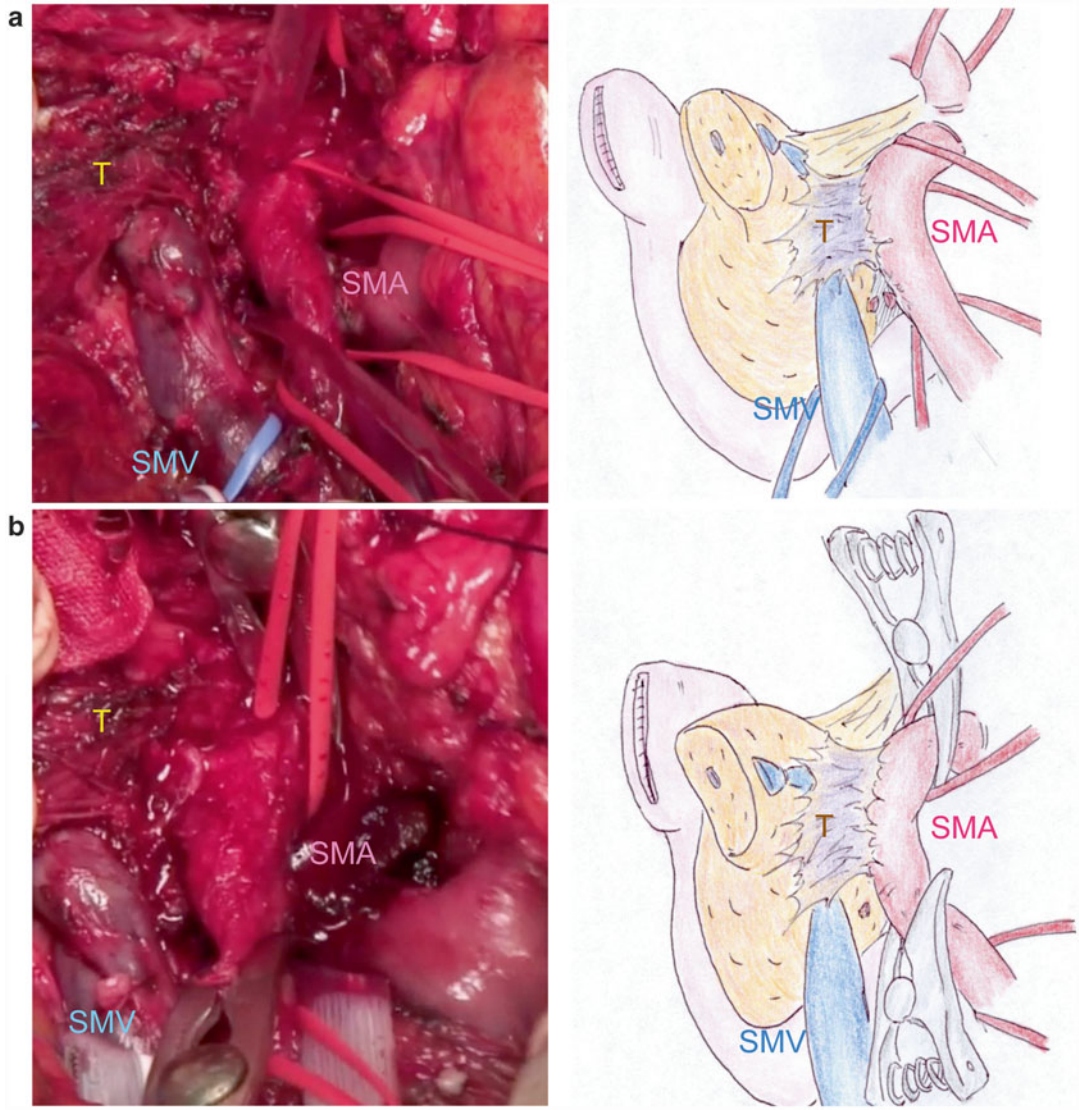

Fig. 17.13 Anterior approach to the SMA in a case of the tumor abutting and surrounding nearly 180°. Operation photos and schemas of a 60-year-old man with BR-A who underwent curative-intent resection after CRT. After exposing the anterior wall of SMA toward its root, vascular tapes were encircled distal and proximal to the site of severe tumor abutment (**a**). Thereafter, vascular clamps on the SMA were placed proximal and distal to the site involved by the tumor (**b**). *T* tumor, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein

vascular tapes were applied distal and proximal to the site of severe tumor abutment of the SMA (Fig. 17.13a). Thereafter, vascular clamps on the SMA were placed proximally and distally (Fig. 17.13b). The right lateral aspect of the SMA was subsequently dissected from the tumor using electrocautery (Fig. 17.14a). The SMA was safely detached from the tumor without injuring it and the vascular clamps were released (Fig. 17.14b). Katz et al. [19] have also emphasized that skeletonization of the right lateral aspect of the SMA can be performed safely after acquisition of vascular control above and below the segment of artery involved by tumor. Pathological examination of the resected specimen in this 60-year-old male revealed that the

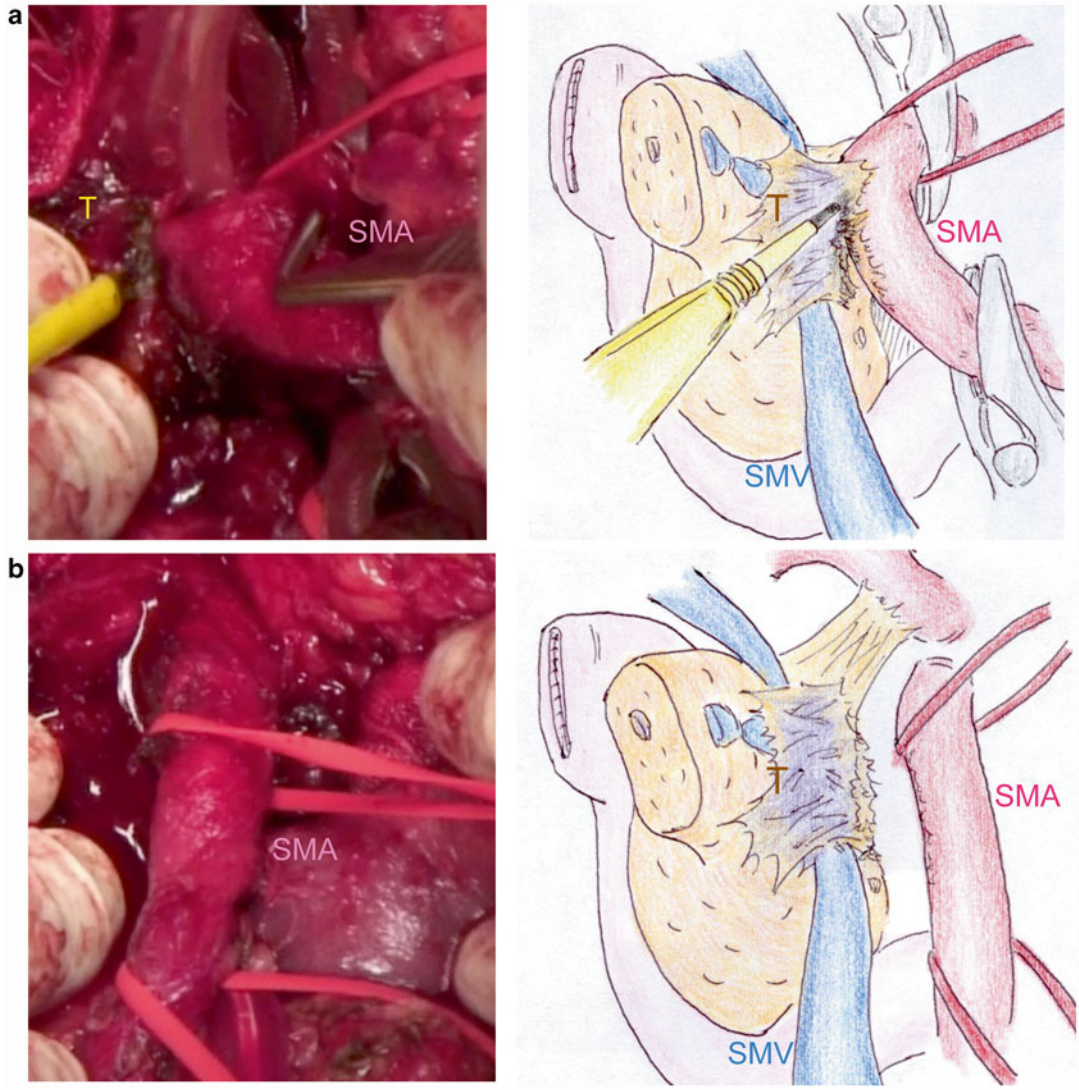

Fig. 17.14 Anterior approach to the SMA in a case of the tumor abutting and surrounding nearly 180° of the vessel. Operation photos and schemas of a 60-year-old man with BR-A who underwent curative-intent resection after CRT. Under keeping vascular clamps on the SMA to control hemorrhage, the right lateral aspect of the SMA was dissected from the tumor using electrocautery (**a**). The SMA was safely detached from the tumor without injuring it and the vascular clamps were released (**b**). *T* tumor, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein

resection margins were microscopically positive (R1) and the tumor showed a grade IIa histological response (10–50 % nonviable tumor cells) according to Evans's histopathological criteria [20]. The patient survived 30 months after PD and ultimately died with lung metastases. In this case, the tumor demonstrated a minimal radiographic response while CA19-9 levels were normalized after CRT. Katz et al. [21] have similarly noted that radiographic downstaging in BR-PDAC has historically been rare following neoadjuvant therapy, and concluded that BR-PDAC patients should undergo pancreatectomy after initial therapy in the absence of metastases.

When BR-PDAC or LUR-PDAC of the head and/or body invades the origin of splenic artery (SA), total pancreatectomy (TP) cannot be

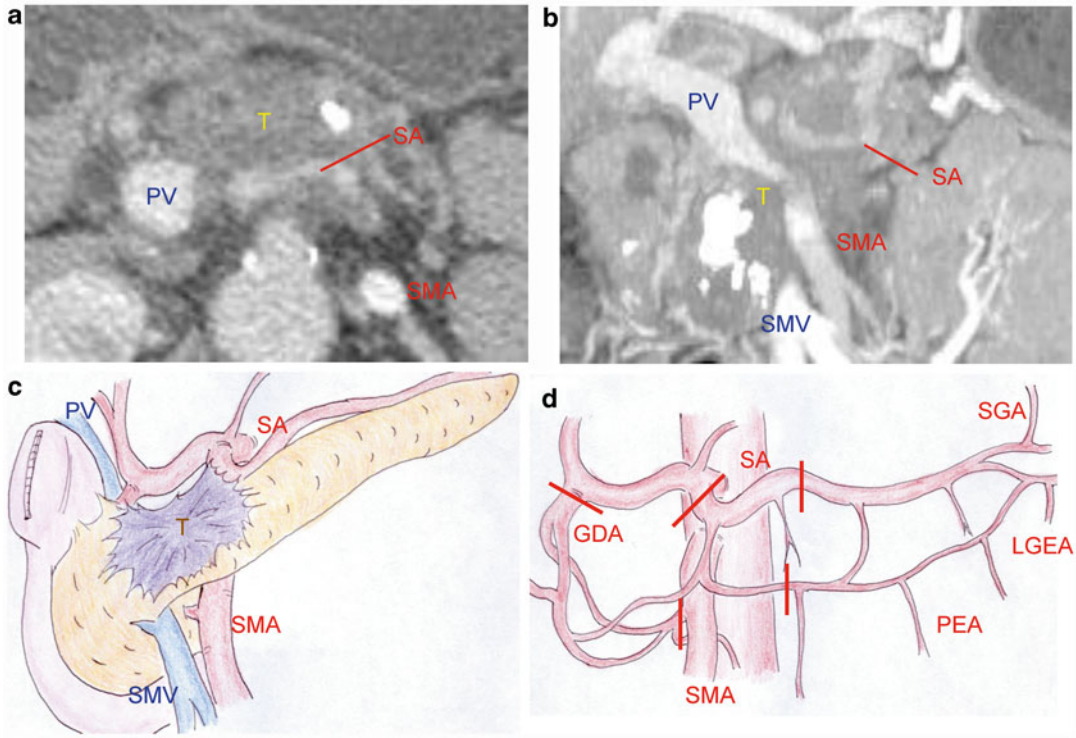

Fig. 17.15 Pancreaticoduodenectomy with splenic artery resection (PD-SAR). CT image of a 64-year-old male with BR-A: cross-sectional image (**a**), coronal reconstruction image (**b**). The tumor (T) encased the PV and SA and abutted the SMA. The schema of the tumor location (**c**). The arterial anatomy around the pancreas (a red line indicates transection sites of arteries in PD-SAR). *BR-A* borderline resectable pancreatic adenocarcinoma with major artery involvement, *T* tumor, *PV* portal vein, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery, *SA* splenic artery, *GDA* gastroduodenal artery, *SGA* short gastric artery, *LGEA* left gastroepiploic artery, *PEA* posterior epiploic artery

avoided because the blood supply to the distal pancreas is removed with division of the origin of SA. The prognosis of PDAC patients following TP is not superior to that of PD patients [22], and TP causes insulin-dependent diabetes mellitus (DM) and exocrine insufficiency, leading to a poor quality of life. For tumors that invade the SA, we developed a new surgical technique of proximal subtotal pancreatectomy with splenic artery and vein resection, the so-called PD with SA resection (PD-SAR). This operation was designed in an attempt to simultaneously maximize operative radicality and postoperative QOL [23]. The operation relies upon blood flow to the pancreas tail being maintained by the left gastroepiploic artery (LGEA) and/or posterior epiploic artery (PEA) even when the left gastric artery (LGA) is sacrificed with total gastrectomy and splenectomy [24].

Figure 17.15 shows CT images of a 64-year-old man with BR-A PDAC: the tumor encased the PV and SA and abutted SMA, so PD-SAR was performed after S1/GEM-CRT. The schema of the tumor location and sites of arterial ligation we used as part of this operation are shown in Fig. 17.15c,d. Reconstruction after subtotal stomach-preserving PD-SAR was performed as shown in Fig. 17.16a,b, and the spleen was preserved. In cases in which the tumor invades the SA and LGA, reconstruction after PD-SAR with total gastrectomy and splenectomy is performed as shown in Fig. 17.16c, d.

We retrospectively reviewed the clinical data of 84 patients who underwent PD for PDAC of the head and/or body between January 2008 (when we performed the first case of PD-SAR) and December 2013. Most of these patients had been treated by preoperative GEM-CRT or

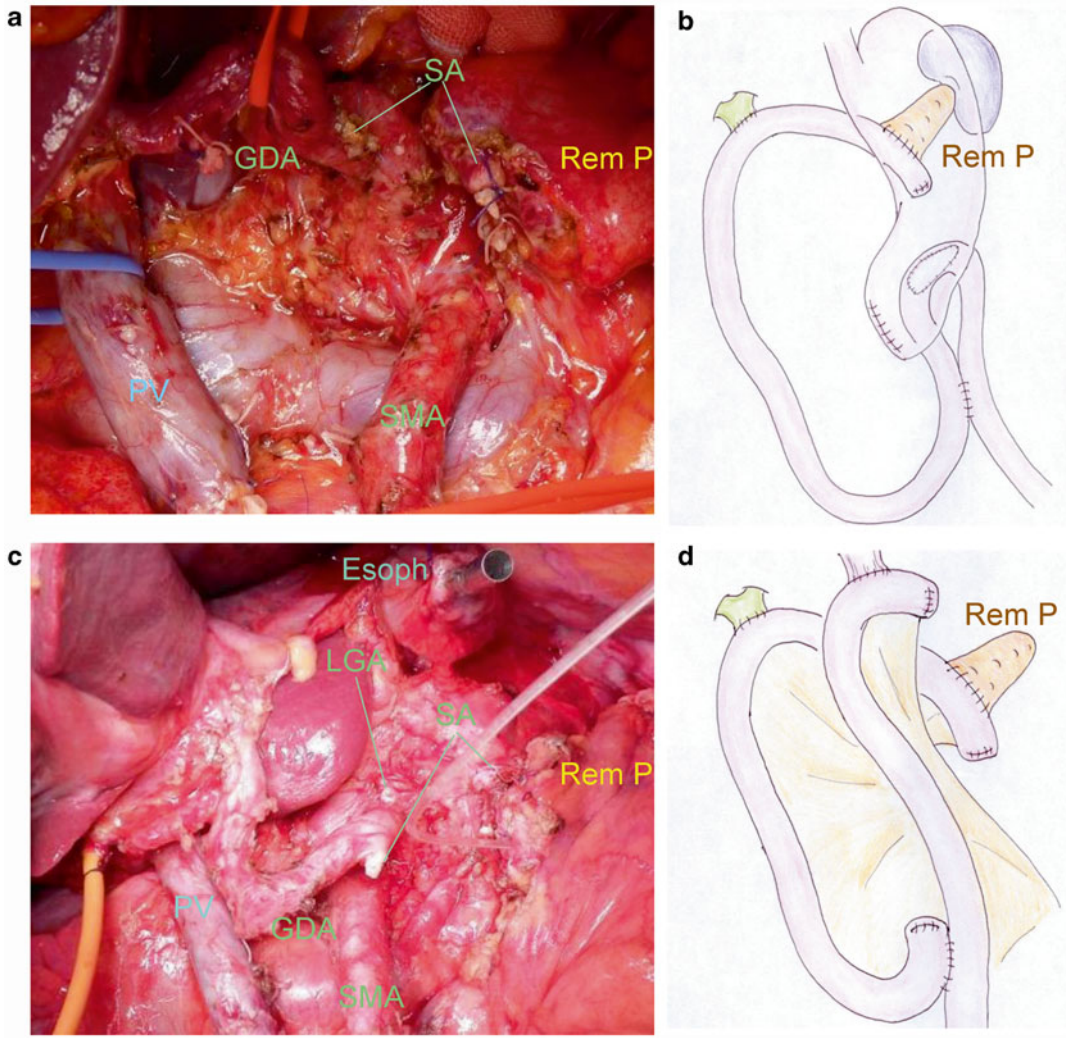

Fig. 17.16 Operation photos and schemas of reconstruction after PD-SAR. Operation photo after PD-SAR: cut ends of proximal and distal sides of the splenic artery (SA) are shown (**a**). Schema of reconstruction after subtotal stomach preserving PD-SAR: spleen is preserved (**b**). Operation photo after PD-SAR with total gastrectomy and splenectomy in case of tumor invasion of the SA and left gastric artery (LGA): cut ends of proximal and distal sides of the splenic artery (SA) and LGA are shown (**c**). Schema of reconstruction after PD-SAR with total gastrectomy and splenectomy. *PV* portal vein, *SMA* superior mesenteric artery, *GDA* gastroduodenal artery, *Rem P* remnant pancreas, *Esoph* cut end of the esophagus

S1/GEM-CRT [23]. Three-year survival rates were very similar between patients who underwent PD ($n=66$) and PD-SAR ($n=18$): 23.7 % vs. 23.1 % ($P=0.538$), even though the median tumor size and the percentages of T4 tumor determined before treatment were higher in PD-SAR. The total daily insulin dose at 1 month of patients who underwent PD-SAR was significantly higher than that of patients who underwent PD, but there was no significant difference thereafter in this regard. It was therefore concluded that PD-SAR with preoperative CRT seemed to be promising surgical strategy for PDAC of head and/or body with invasion of the SA.

Locally Unresectable Pancreatic Ductal Adenocarcinoma

Multi-Institutional Survey in Japan

Some candidates for surgical resection exist among patients with initially unresectable PDAC who are treated initially with nonoperative therapy. Surgical resection of such patients after a favorable response has been referred to as "adjuvant surgery" [25]. Since the role of adjuvant surgery for LUR-PDAC or metastatic PDAC has been poorly studied because of lack of large number of such patients, the clinical data on initially unresectable PDAC patients with a favorable response to CRT and/or chemotherapy over 6 months from 2001 to 2009 were collected as a project study of pancreatic surgery under the supervision of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) [26]. Detailed data from 58 patients with unresectable cancer who received "adjuvant surgery" following nonoperative therapies were retrospectively collected from 39 out of 150 training institutes for highly advanced surgery registered by the committee of the JSHBPS in 2009. Clinical data from 101 patients who initially presented with unresectable PDAC, had a favorable long-term response to nonsurgical anticancer treatments, and who did not subsequently undergo surgical resection were also collected as a comparison group from the same 39 centers. All patients had cytologically or pathologically proven PDAC; the unresectability of PDAC was based on the clinical criteria used in each institute. The reason patients were characterized as having unresectable PDAC was a locally advanced primary tumor in 41 patients (70.7 %) and distant metastases in 17 (29.3 %) in the adjuvant surgery group; and in the control group, it was a locally advanced primary tumor in 59 (58.4 %) and distant metastases in 42 (41.6 %). Propensity scores were calculated using multivariate logistic regression with calculation of the conditional probabilities for the adjuvant surgery group to adjust for the significant differences in the clinical backgrounds between the two groups.

Survival of the adjuvant surgery group was significantly more favorable than that in the comparison group ($P<0.0001$): the 1-, 3-, and 5-year survival rates following initial treatment were 95 %, 53 %, and 34 %, respectively, in the adjuvant surgery group (MST:39.7 months); and they were 88 %, 18 %, and 10 %, respectively, in the comparison group (MST: 20.8 months). The propensity score analysis revealed that adjuvant surgery was a significant independent prognostic variable. Subgroup analysis according to the time from initial treatment to surgical resection showed a significant difference in the overall survival of patients who underwent resection over 240 days after the initial treatment. In contrast, there was no difference in the survival curves between the patients who underwent resection between 180 and 240 days after initial treatment and those in the comparison group. It was therefore concluded that adjuvant surgery for initially unresectable PDAC patients with a long-term favorable response to nonsurgical anticancer treatments, especially for more than 240 days, was a safe and effective treatment.

Outcomes of Chemoradiotherapy Followed by Surgery (CRT-S) in Our Institution

In an attempt to determine the effect of CRT-S on the resection rate and survival of patients with primarily unresectable locally advanced PDAC, Morganti et al. [27] conducted a systematic review of the recent literature. Only studies published after the year 2000 and which examined radiotherapy regimens employing standard dose and fractionation were analyzed. According to the 13 studies with a total of 510 patients who met selection criteria, the resection rate after CRT-S was 8.3–64.2 % (median, 26.5 %). Among the patients who underwent resection, the R0 resection rate was 57.1–100 % (median, 87.5 %) and pathological complete response was found in 3.0–8.8 %. When the outcome of all patients was considered, median survival ranged from 9 to 23 (median, 13.3) months, comparing favorably

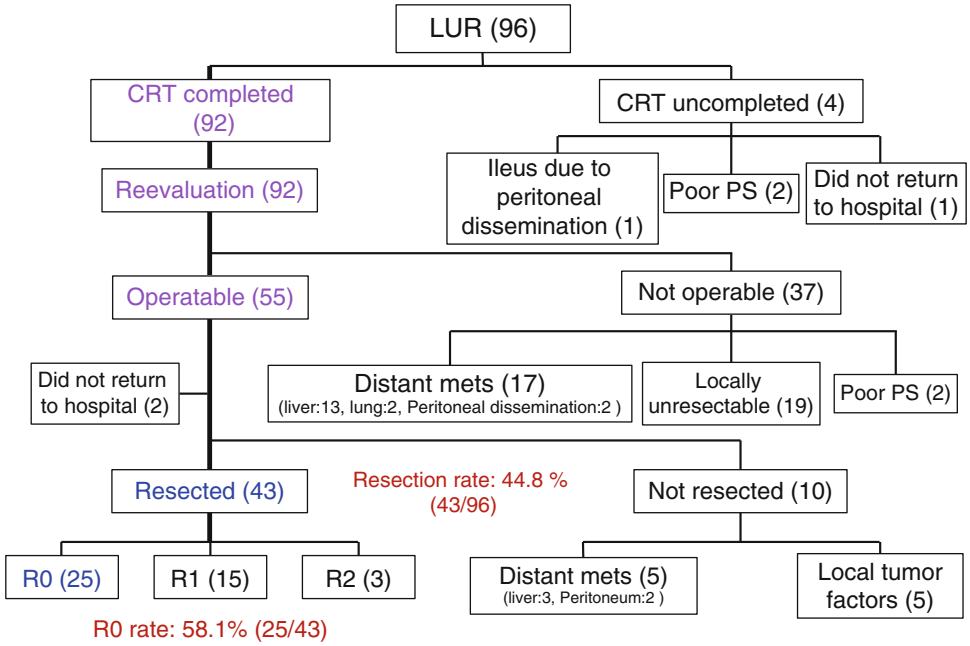

Fig. 17.17 Flow diagram of the patients with locally unresectable pancreatic ductal adenocarcinoma (LUR-PDAC) who had been enrolled for treatment protocol of chemoradiotherapy followed by surgery at Mie University Hospital from February 2005 to September 2014. *CRT* chemoradiotherapy, *PS* performance status, *mets* metastases

with literature data based on CRT alone (range, 8.6–13 months). Surprisingly, the median survival after resection ranged from 16.4 to 32.3 (median, 23.6) months. Based on these data, the authors concluded that patients with unresectable pancreatic cancer without disease progression after CRT should be considered for radical surgery.

As shown in the flow diagram of 96 patients with LUR-PDAC who had been enrolled for treatment using CRT-S in our institution between February 2005 and September 2014 (Fig. 17.17), 92 patients completed CRT and were reevaluated for the possibility of resection. At the time of reassessment, we determined that curative-intent resection was possible when the following findings on MDCT were observed: no stenosis or change of shape in the CA and SMA as well as the absence of metastatic lesions in other distant organs [7]. Intraoperatively, curative-intent resection was not performed when distant metastatic disease was detected on histological examination of frozen sections of suspicious lesions and of distant lymph nodes, including paraaortic lymph nodes. Curative-intent resection was likewise not performed when the primary tumor was found to be considerably locally advanced, showing unreconstructable PV/SMV occlusion even if an external iliac vein graft had been used and/or a severe tumor invasion around the SMA was evident. Among 92 patients who were reassessed for resectability, 55 (59.8 %) were determined to be operable and finally 43 underwent curative-intent resection. R status included R0 in 25 patients (58.1 %), R1 in 15, and R2 in 3.

The distribution of the number of the 43 patients with LUR-PDAC who underwent curative-intent resection was plotted according to the time from the start of CRT to operative resection in Fig. 17.18. The time from initial treatment to surgical resection ranged from 2 months to 28 months (median 96 days), which was significantly shorter compared to that reported in a project study for pancreatic surgery by the JSHBPS [25]. When we analyzed survival curves in the 43 patients who underwent curative-intent resection according to R status and in the 53 patients with

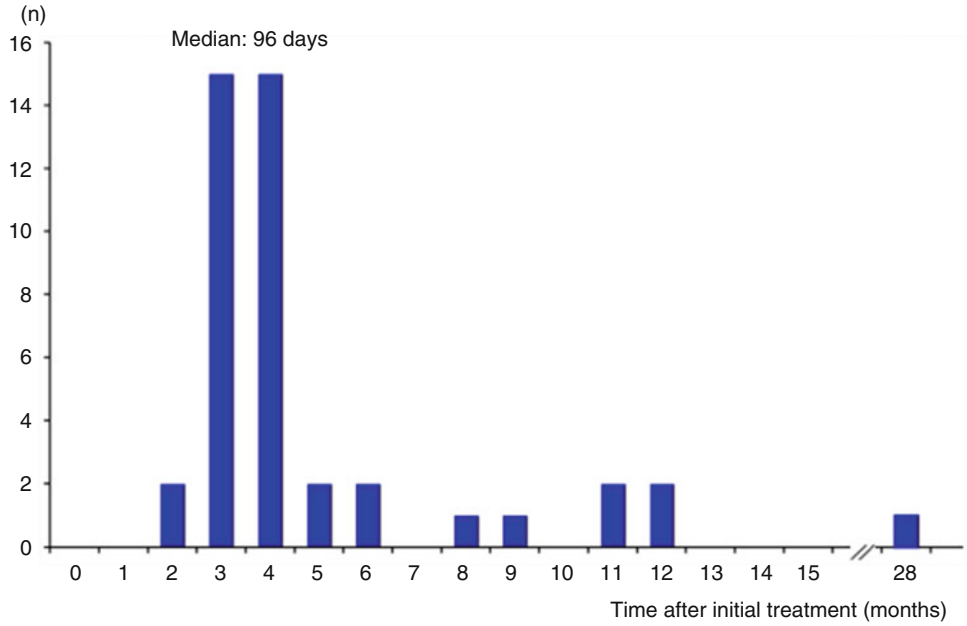

Fig. 17.18 The distribution of the number of the 43 patients with LUR-PDAC who underwent curative-intent resection according to the time from the start of CRT to operative resection. *LUR-PDAC* locally unresectable pancreatic ductal adenocarcinoma, *n* number of patients

no resection (Fig. 17.19), the MST after initial treatment of patients who underwent R0 resection was 21.2 months, of patients who underwent R1 resection was 19.9 months, of patients who underwent R2 resection was 16.0 months, and was 10.1 months in the patients who did not undergo resection, showing significant difference between patients who underwent R0 and those who did not undergo resection ($P=0.005$).

CT images of a 54-year-old female with LUR-PDAC before CRT and at 12 months after the beginning of CRT followed by chemotherapy are shown in Fig. 17.20. Before CRT, the tumor abutted the SMA over nearly 360° of its circumference (cross section image) and the SMA was poorly visualized (coronal image). Twelve months after the beginning of CRT followed by chemotherapy, the tumor size was significantly decreased and the SMA was well visualized (coronal image), and the serum CA19-9 level had significantly decreased from 2470 to 24 U/m. Resected specimens in this patient are shown in Fig. 17.21. Pathologically, histological response to CRT followed by chemotherapy was determined as grade III (tumor destruction of 90 % or more) according to the Evan histological criteria [20], showing residual tumor size of 12 by 7 mm. This patient is alive without tumor recurrence at 21 months after resection at the time of this writing.

We concluded that our CRT-S protocol for LUR-PDAC allowed for the identification of candidates for aggressive resection at the time of reassessment and improved prognosis in the patients who achieved R0 resection. Our previous study [7] compared survival curves according to hENT1 expression of the resected specimen in BR-PDAC and LUR-PDAC patients. The 3-year survival rate was not significantly different between positive and negative hENT1 expressions (37.2 % vs. 22.2 %) in the BR group, whereas in the LUR group the 3-year survival rate was significantly higher in patients whose tumors expressed hENT1 than those with tumors which did not express hENT1: 11.9 % vs. 0 % (MST: 22.8 months vs. 10.6 months, $P=0.003$). Therefore, pretreatment evaluation of hENT1 expression in PDAC tissue can be beneficial in

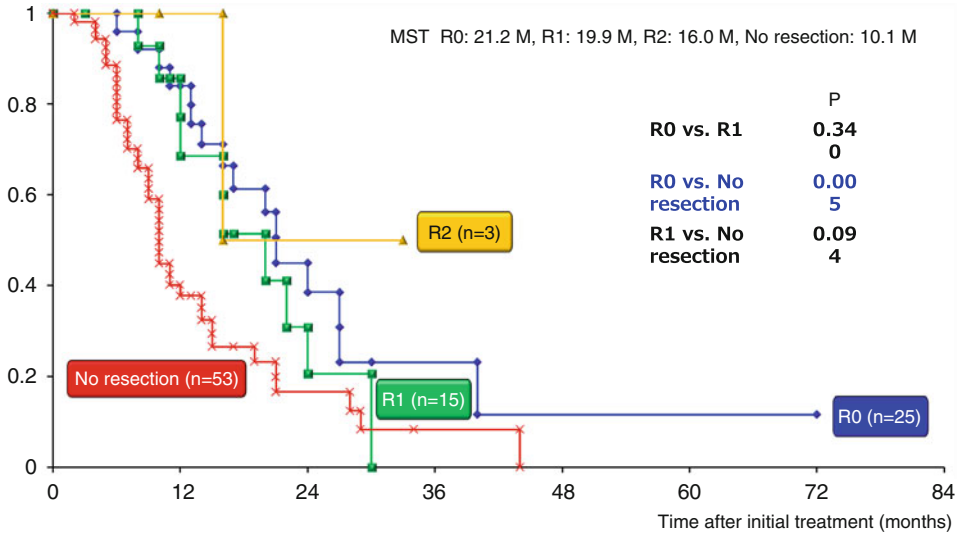

Fig. 17.19 Kaplan–Meier survival curves in the 43 patients with LUR-PDAC who underwent curative-intent resection according to R status and in the 53 patients with no resection. *LUR-PDAC* locally unresectable pancreatic ductal adenocarcinoma, *MST* median survival time

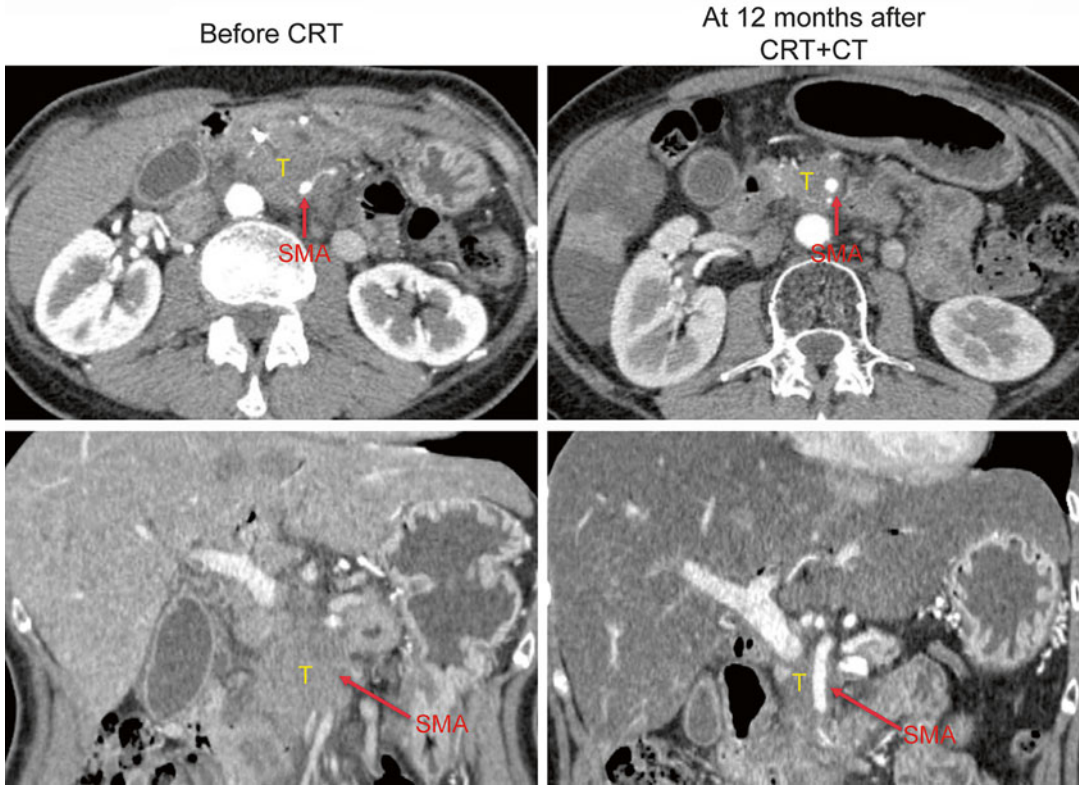

Fig. 17.20 CT images of a 54-year-old female with LUR-PDAC before CRT and at 12 months after the beginning of CRT followed by chemotherapy. Before CRT, the tumor abutted the SMA nearly 360° of its circumference (cross section image) and the SMA was poorly visualized (coronal image). At 12 months after the beginning of CRT followed by CT, the tumor size was significantly decreased and the SMA was well visualized (coronal image), and serum CA19-9 levels significantly decreased from 2470 to 24 U/m. *T* tumor, *SMA* superior mesenteric artery, *LUR-PDAC* locally unresectable pancreatic ductal adenocarcinoma, *CRT* chemoradiotherapy, *CT* chemotherapy

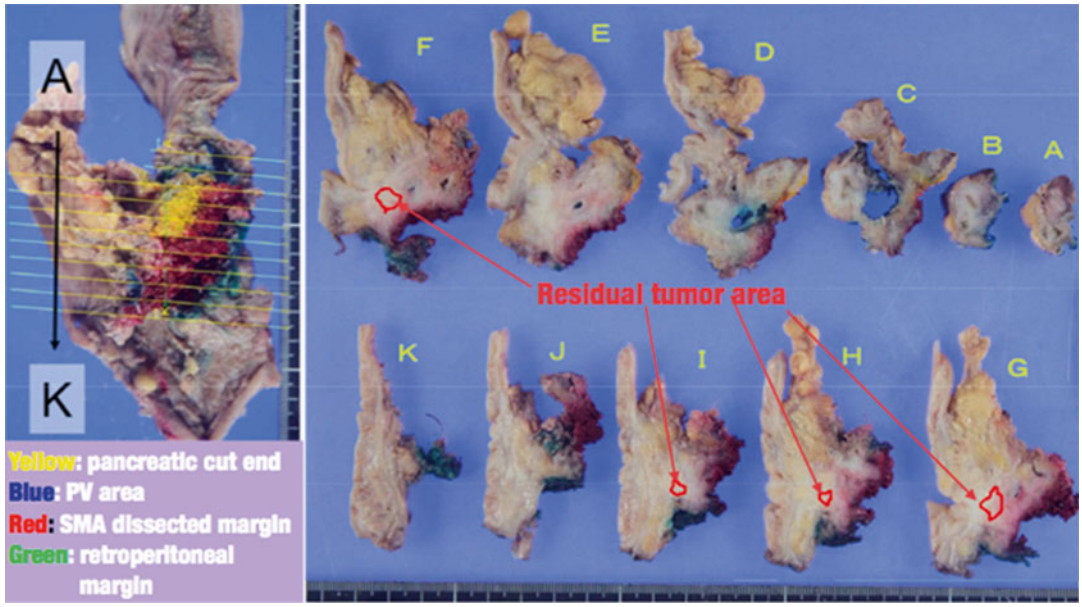

Fig. 17.21 Resected specimens in a 54-year-old female with LUR-PDAC who underwent curative-intent resection at 12 months after the beginning of CRT followed by CT. Pathologically, histological response to CRT followed by CT was determined as grade III (tumor destruction of 90 % or more) according to the Evan histological criteria, showing residual tumor size of 12 by 7 mm. *PV* portal vein, *SMA* superior mesenteric artery, *LUR-PDAC* locally unresectable pancreatic ductal adenocarcinoma, *CRT* chemoradiotherapy, *CT* chemotherapy

predicting the efficacy of GEM-based therapy before initial treatment. Our previous data provided the evidence that intratumoral hENT1 expression in EUS-FNA samples could be used to predict the treatment outcome of GEM-CRT, although improvement in the rate of acquisition of specimens by EUS-FNB and further modification of the protocol for the assay of hENT1 were required.

Conclusion

BR-PDAC includes two distinct categories of tumors: BR-PV (those with PV/SMV invasion alone) and BR-A (those with major arterial invasion). Our GEM-CRT and S1/GEM-CRT protocols for BR-PDAC appeared to improve survival, especially in the patients with BR-A tumors, by enhancing R0 resection rate. Adjuvant surgery for initially unresectable PDAC patients with a long-term favorable response to nonsurgical anticancer treatments is safe and effective. Our CRT-S protocol for LUR-PDAC may also allow for the identification of candidates for aggressive resection at the time of reassessment and to improve prognosis of patients who undergo R0 resection.

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18 The Role of Irreversible Electroporation and Other Ablative Techniques in Patients with Borderline Resectable Pancreatic Cancer

Robert C.G. Martin II and Rachel O'Connor

Introduction

Pancreatic ductal adenocarcinoma is one of the most aggressive cancers and is the fourth leading cause of cancer death in the western world [1]. Locally advanced disease is difficult to control, and limited improvement in outcomes has been achieved in the last 30 years despite the advances in diagnostic and treatment modalities. For all stages combined, the 1-year survival rate is 20 %, and the overall 5-year survival rate has remained dismally poor at 5 % [2]. Complete surgical resection remains the only curative treatment for pancreatic cancer. The advanced T-stage of pancreatic adenocarcinoma is defined on the basis of significant involvement of the superior mesenteric artery and celiac axis, and/or segmental portal vein occlusion, on cross-sectional imaging [3, 4].

Pancreatic tumors become symptomatic only at a very advanced stage; therefore, only a small percentage (15–20 %) of patients qualifies for surgical resection. In the rest of the patients, there might be either advanced locoregional disease without distant metastases (expected survival of 6–12 months) or locoregional disease with distant metastases (expected survival of 3–6 months) [5]. Chemoradiation therapy (CRT) provides short-term disease control and may offer a modest survival benefit of 3 months [6, 7]. The recent combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)—demonstrated better response and survival rates in this specific subgroups (Stage 3) of patients; however, long-term results from ongoing trials are not yet available [8]. The usefulness of radiation therapy was also tested; however, the results were not significant [7, 9].

Considering the limited duration of effect of CRT, there is a clear need for an adjunctive or consolidative local treatment to provide greater durable local control to provide pain control, which could possibly improve overall survival in patients with LAPC. Image-guided ablation techniques, such as radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE), have been proposed as new treatment options in such cases.

Local Ablative Therapies

When local ablative therapies are applied, chemical, thermal, or electrical energy is transferred to a specific area of soft tissue with the intent of complete tissue destruction or ablation.

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Chemical ablation includes the use of ethanol or acetic acid, which induces coagulation necrosis of the tumor mass after direct injection/contact with these agents (Tables 18.1, 18.2, 18.3, and 18.4). With chemical ablation, there is always the risk of migration/injection into the arterial system with fatal consequences, and its application in the treatment of locally advanced pancreatic cancer is therefore limited [10].

Thermal ablation is based on the increase or the decrease of tumor temperature. When heat is applied, a target temperature of 50 °C (particularly temperatures ranging from 60 to 100 °C or more) results in tissue thermal injury and tumor ablation. The method of cell death results from apoptosis and eventually coagulative necrosis. Cold temperatures can also be utilized to ablate tumors (cryoablation), temperatures lower than the tissue freezing edge (i.e., temperature lower than −40 °C,) can cause necrosis of target cells [11, 12]. There are several thermal ablation studies on the treatment of pancreatic cancer, mainly with the use of applied heat. Very few studies have evaluated the use of cryotherapy for the management of locally advanced pancreas cancer.

Electrical current ablation is a technology that is based on the irreversible increase of permeability of the cellular membrane with the use of high voltage (3000 V), short pulse (70–90 μs) electric currents (IRE). IRE is one of the latest technological advances, and recent studies have been performed on its application in the local treatment of pancreatic cancer. Improvements in intraoperative imaging, electrodes, and ultrasound (US) technology have enabled the technology to accurately treat tumors [13–15]. IRE has been applied to patients who are not considered suitable for surgical resection and have failed previous therapy with chemoradiotherapy. IRE may offer consolidative disease control, with symptom relief, control of pain, and definitive eradication of the lesion.

The inherent limitation for local ablative therapy of the pancreas is the heterogeneity of the tissue and the surrounding structures, as these can be damaged and lead to complications such as pancreatitis, vascular thrombosis, or enteric injury.

Radiofrequency Ablation

The first initial report of the use of RFA in an animal model was by Goldberg et al. [16] who reported that RFA could be used safely and effectively. This conclusion was extrapolated to the clinical scenario of small neuroendocrine tumors and possibly in the palliation of LAPC. An additional report from Date et al. [17] reported the safety of RFA in a normal pancreas of a porcine model. The first clinical report on 20 patients was published by Matsui et al. [18] in 2000 (Table 18.5). Since then, several case reports have been published from various groups of investigators [19–22] (Table 18.3). The use of RFA in the pancreas has been recently summarized in a systematic review in the treatment of LAPC [19]. Five cohort studies (four prospective and one retrospective) were reported through 2012. This report did not include reports of < five cases and included only studies that reported RFA of pancreatic adenocarcinoma. A total 158 patients were treated with four different ablation devices: 100 patients using a 1500× generator (RITA Medical Systems, Mountain View, CA), 28 patients using a Radionics generator (Radionics Inc., Burlington, MA), 10 patients using a generator manufactured by Berchtold GmbH & Co., KG (Tuttlingen Germany), and 20 patients using a generator manufactured by Omron Co., Ltd (Kyoto, Japan). In the initial study by Matsui et al. [18], the technique they utilized was a controlled ablation of 50 °C for 15 min using 4 needles and reported a median overall survival of 3 months. Matsui's poor survival outcomes may have been related to the fact that they included patients with metastatic disease. Overall survival was reported to be better in two additional studies at 20 months [20] and 33 months, respectively [21]. A systematic review by Singh et al. [23] reported an overall survival range of 9–36 months. The largest series published to date was from Girelli et al. [20]. In this series of 100 patients, a morbidity of 15 % and mortality of 3 % was reported. The authors utilized extreme heat (105 °C) in the first 25 patients leading to significant vascular and intestinal injury. They then modified their technique

Table 18.1 Use of chemical ablative therapies to treat cystic and solid premalignant lesions of the pancreas

Author	Premalignant lesion	*n*	Treatment	Median area of ablation, mm (range)	Outcome	Complications
Gan, et al.	Cystic tumors of the pancreas	25	EUS-guided ethanol lavage	19.4 (6–30)	Complete resolution in 35 %	None
Oh, et al.	Cystic tumors of the pancreas	14	EUS-guided ethanol lavage + paclitaxel	25.5 (17–52)	Complete resolution in 79 %	Acute pancreatitis ($n=1$)
						Hyperamylasemia ($n=6$)
						Abdominal pain ($n+1$)
Oh, et al.	Cystic tumors of the pancreas	10	EUS-guided ethanol lavage + paclitaxel	29.5 (17–52)	Complete resolution in 60 %	Mild pancreatitis ($n=1$)
DeWitt, et al.	Cystic tumors of the pancreas	42	Randomized double blind study: Saline vs. ethanol	22.4 (20–68)	Complete resolution in 33 %	Abdominal pain at 7 d ($n=5$)
						Pancreatitis ($n=1$)
						Acystic bleeding ($n=1$)
Oh, et al.	Cystic tumors of the pancreas	52	EUS-guided ethanol lavage + paclitaxel	31.8 (17–68)	Complete resolution in 62 %	Fever (1.52)
						Mild pancreatitis (1/52)
						Splenic vein obliteration (1/52)
Levy, et al.	PNET	8	EUS-guided ethanol lavage (5 patients) and intraoperative ultrasound-guided (IOUS) ethanol lavage (3 patients)	16.6 (8–21)	Hypoglycemia symptoms disappeared 5/8 and significantly improved 3/8	EUS guided: No complications
						IOUS-guided ethanol injection: Minor peritumoral bleeding (1/3), pseudocyst (1/3)
Pai, et al.	Cystic tumors of the pancreas + neuroendocrine tumors	8	EUS-guided RFA	Mean size pre-RFA, 38.8 mm vs. mean size post-RFA, 20 mm	Complete resolution in 25 % (2/8)	2/8 patients had mild abdominal pain that resolved in 3 days

RFA radiofrequency ablation, *EUS* endoscopic ultrasound, *PNET* pancreatic neuroendocrine tumor

Table 18.2 Endoscopic ultrasound administered non-ablative and antitumor therapies for pancreatic ductal adenocarcinoma

Author	Therapy	Patients	*n*	Outcome and survival	Complications
Chang, et al.	Cytoimplant (mixed lymphocyte culture)	Unresectable PDAC	8	Median survival: 13.2 months. 2 partial responders and 1 minor response	7/8 developed low-grade fever 3/8 required biliary stent placement
Hecht, et al.	ONYX-015 (55-kDa gene-deleted adenovirus) + IV gemcitabine	Unresectable PDAC	21	No patient showed tumor regression at day 35. After commencement of gemcitabine, 2/15 had a partial response	Sepsis: 2/15, duodenal perforation: 2/15
Hecht, et al. Chang, et al.	TNFerade (replication-deficient adenovector containing human tumor necrosis factor (TNF)-a gene)	Locally advanced PDAC	50	Response: One complete response, 3 partial responses. 7 patients eventually went to surgery, 6 had clear margins and 3 survived >24 months	Dose-limiting toxicities of pancreatitis and cholangitis were observed in 3/50
Herman, et al.	Phase III study of standard care plus TNFerade (SOC + TNFerade) vs. standard of care alone (SOC)	Locally advanced PDAC	304 (187 SOC + TNFerade)	Median survival: 10.0 months for patients in both the SOC + TNFerade and SOC arms [hazard ratio (HR), 0.90, 95 % Cl; 0,66–1.22, *P*—0.26]	No major complications. Patients in the SOC+TNFerade arm experienced more grade 1–2 fever than those in the SOC alone arm ($p < 0.001$)
Sun, et al.	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	15	Tumor response: "partial" in 27 % and "minimal" in 205. Pain relief: 30 %	Local complications (pancreatitis and pseudocyst formation) 3/15. Grade III hematologic toxicity in 3/15
Jin, et al.	EUS-guided implantation of radioactive seeds (iodine-125)	Unresectable PDAC	22	Tumor response: "partial" in 3/22 (13.6 %)	No complications

PDAC pancreatic ductal adenocarcinoma, *EUS* endoscopic ultrasound

Table 18.3 Studies of cryoablation in pancreatic ductal adenocarcinoma

Study	*n*	Patients	Study	Outcome	Complications
Patiutko et al. (non-English article)	30	Locally advanced PDAC	Combination of cryosurgery and radiation	Pain relief and improvement in performance status 30/30	Not reported
Kovach et al.	9	Unresectable PDAC	Phase I study of intraoperative cryoablation under US guidance; 4 had concurrent gastrojejunostomy	7/9 discharge with non-intravenous analgesia and 2/9 discharged with no analgesia	No complications reported
Li et al. (non-English article)	44	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 14 months	40.9 % (18/44) had delayed gastric emptying. 6.8 % (3/44) had a bile and pancreatic leak
Wu et al. (non-English article)	15	Unresectable PDAC	Intraoperative cryoablation under US guidance	Median overall survival: 13.4 months	1/15 patients developed a bile leak
Yi et al. (non-English article)	8	Unresectable PDAC	Intraoperative cryoablation under US guidance	Not reported	25 % (2/8) developed delayed gastric emptying
Xu et al.	38	Locally advanced PDAC, 8 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance + (125) iodine seed implantation	Median overall survival: 12 months. 19/38 (50,9 %) survived more than 12 months	Acute pancreatitis: 5/38 (one has severe pancreatitis)
Xu et al.	49	Locally advanced PDAC, 12 had liver metastases	Intraoperative or percutaneous cryoablation under US or CT guidance + (125) iodine seed implantation. Some pts also received regional celiac artery chemotherapy	Median survival: 16.2 months. 26 patients (53.1 %) survived more than 12 months	Acute pancreatitis: 6/49 (one had severe pancreatitis)
Li et al.	68	Unresectable PDAC requiring palliative bypass	Retrospective case series of intraoperative cryoablation under US guidance, followed by palliative bypass	Median overall survival: 30.4 months (range 6–49 months)	Postoperative morbidity: 42.9 %
					Delayed gastric emptying occurred in 35.7 %
Xu et al.	59	Unresectable PDAC	Intraoperative or percutaneous cryotherapy	Overall survival at 12 months: 34.5 %	Mild abdominal pain: 45/59 (76.3 %)
					Major complications (bleeding, pancreatic leak): 3/59 (5 %)
Niu et al.	36 (CT)	Metastatic PDAC	Intraoperative cryotherapy (CT) or cryo-immunotherapy (CIT) under US guidance	Median overall survival in	Not reported
	31 (CIT)			CIT: 13 months	
				CT: 7 months	

Table 18.4 Studies of photodynamic therapy in pancreatic ductal adenocarcinoma

Study	*n*	Study	Photosensitizer	Number of fibers	Number of ablations	Outcome and survival	Complications
Brown et al.	16	CT-guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	mTH-PC	1	Single	Tumor necrosis: 16/16 Median survival: 9.5 months. 44 % (7/16) survived > 1 year	Significant gastrointestinal bleeding: 2/16 (controlled without surgery)
Huggett et al.	13 + 2	CT-guided percutaneous PDT to locally advanced but inoperable PDAC without metastatic disease	Verteporfin	1	Single (13) Multiple (2)	Technically feasible: 15/15. Dose-dependent necrosis occurred	Single fiber: No complications. Multiple fibers: CT evidence of inflammatory change anterior to the pancreas, no clinical sequellae

PDAC pancreatic ductal adenocarcinoma

slightly with target temperatures of 90 °C. Others have also reported significant morbidity and mortality rates. Wu et al. reported a morbidity of 38 % and mortality of 25 % [22]. These results were related to three patients developing a pancreatic fistulas, three having massive gastrointestinal bleeding after portal vein thrombosis, with four procedure-related deaths. These results demonstrate that the use of a coagulative temperature will not only result in necrosis of the tumor, but also of the surrounding soft tissue(s). In an attempt to minimize these complications, several authors have described using cooling devices inserted endoscopically into the duodenum [24]. Similar intraoperative cooling devices have also been utilized as reported by Cavallini et al. [25] with encouraging results.

Interpretation of the results associated with RFA ablation is difficult based on the heterogeneity of the patient population treated and the variation of the RFA settings and protocols utilized. Currently, the use of any type of thermal injury-based coagulative necrosis-inducing therapy should be avoided and has limited utilization in the treatment of LAPC based on the high morbidity and mortality rates reported. The rationale that RFA appears to be feasible is misguided.

Microwave Ablation

Microwave ablation (MW) is a newer thermal-based ablation technique that utilizes frequencies between 915 and 2450 MHz, which lie between the infrared radiation and radio waves frequencies [26, 27]. The key method of action is based on the agitation of water molecules, which induces rapid heating (>100 °C within 30–45 s), thus inducing cellular death by coagulation necrosis. This efficiency of heating is based on the electrical charge of the water molecule, which flip back and forth 2–5 billion times a second depending on the frequency of the microwave energy [28, 29]. The key differences and advantages of MWA include the significantly greater intratumoral temperatures that are achieved, the larger volumes of ablation that can be achieved, rapid ablation times, the use simultaneously placed multiple applicators, and optimal heating close to vascular structures, thus bypassing the heat-sink effect [28–31].

The first reported application of MWA in pancreatic tumors was published by Lygidakis et al. [32] who reported on 15 patients who underwent MWA of their pancreatic tumors through an intraoperative approach. They reported partial

Table 18.5 Studies of radiofrequency ablation in pancreatic ductal adenocarcinoma

Study	Patients	*n*	Route of administration	Device	RFA temp	RFA duration (min)	Outcome	Complication
Matsui, et al.	Unresectable PDAC	20 LA:9 M:11	At laparotomy 4 RFA probes were inserted into the tumor 2 cm apart	A 13.56-MHz RFA pulse was produced by the heating apparatus	50	15	Survival: 3 months	Mortality: 10 % (septic shock and gastrointestinal bleeding)
Hadjicostas, et al.	Locally advanced and unresectable PDAC	4	Intraoperative—followed by palliative bypass surgery	Cool-tip™ RFAblation system	NR	2–8	All patients were alive 1-year post-RFA	No complications encountered
Wu, et al.	Unresectable PDAC	16 LA:11 M:5	Intraoperative	Cool-tip™ RFAblation system	30–90	12 at 30 °C then 1 at 90 °C	Pain relief: back pain improved (6/12)	Mortality: 25 % (4/16 Pancreatic fistula: 18.8 % (3/16)
Spiliotis, et al.	Stage III and IV PDAC receiving palliative therapy	12 LA: 8 M:4	Intraoperative—followed by palliative bypass surgery	Cool-tip™ RFAblation system	90	5–7	Mean survival: 33 months	Morbidity:16 % (biliary leak) Mortality: 0 %
Girelli, et al.	Unresectable locally advanced PDAC	50	Intraoperative—followed by palliative bypass surgery	Cool-tip™ RFAblation system	105 (25 pts) 90 (25 pts)	Not reported	Not reported	Morbidity 40 % in the first 25 patients. Probe temperature decreased from 105 to 90 °C. Morbidity 8 % in second cohort of 25 patients 30-day mortality: 2 %
Girelli, et al.	Unresectable locally advanced PDAC	100	Intraoperative—followed by palliative bypass surgery	Cool-tip™ RFAblation system	90	56–10	Median overall survival: 20 months	Morbidity: 15 %. Mortality: 3 %

(continued)

Table 18.5 (continued)

Study	Patients	*n*	Route of administration	Device	RFA temp	RFA duration (min)	Outcome	Complication
Giardino, et al.	Unresectable PDAC, 47 RFA alone, 60 had RFA + RCT and/or IASC	107	Intraoperative—followed by palliative bypass surgery	Cool-tip™ RFAblation system	90	5–10	Median overall survival: 14.7 months in RFA alone but 25.6 months in those receiving RFA + RCT and/or IADC ($p = 0.004$)	Mortality 1,8 % (liver failure and duodenal perforation) Morbidity: 28 %
Arcidiacono et al.	Locally advanced PDAC	22	EUS guided	Cryotherm probe; bipolar RFA + cryogenic cooling	NR	2–15	Feasible in 16/22 (72.8 %)	Pain (3/22)
Steel et al.	Unresectable malignant bile duct obstruction (16/22 due to PDAC)	22	RFA + SEMS placement at ERCP	Habib EndoHPB wire-guided catheter	NR	Sequential 2 min treatments—median 2 (range 1–4)	Neduab syrvuvakL 5 ni Successful biliary decompression 21/22	Minor bleeding (1/22) Asymptomatic biochemical pancreatitis (1/22), percutaneous gallbladder drainage (2/22). At 90-day, 2/22 had died, one with a patent SEMS
Figueroa-Barojas et al.	Unresectable malignant bile duct obstruction (7/20 due to PDAC	20	RFA + SEMS placement at ERCP	Habib EndoHPB wire-guided catheter	NR	Sequential 2 min treatments	SEMS occlusion at 90-day (3/22) bile duct diameter increased by 3.5 mm post-RFA ($p = 0.0001$)	Abdominal pain (5/20), mild post-ERCP pancreatitis and cholecystitis (1/20)
Pai, et al.	Locally advanced PDAC	7	EUS guided	Habib EUS-RFA catheter	NR	Sequential 90s treatments—median 3 (range 2–4)	2/7 tumors decreased in size	Mild pancreatitis: 1/7)

PDAC pancreatic ductal adenocarcinoma, *LA* locally advanced PDAC, *M* metastatic PDAC, *SEMS* self-expanding metal stent, *RFA* radiofrequency ablation, *EUS* endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *IASC* intra-arterial systemic chemotherapy

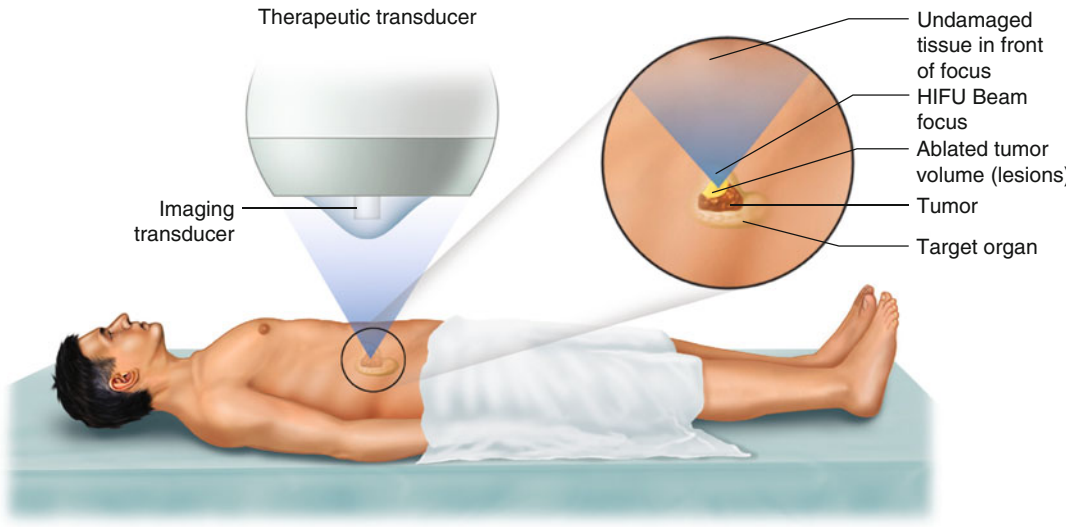

Fig. 18.1 Illustration of extracorporeal high-intensity focused ultrasound treatment of a pancreatic tumor using a transducer that is located above the patient that is in the supine position

necrosis in all treated cases without major complications, but a 40 % incidence of minor complications, including mild pancreatitis, pancreatic ascites, asymptomatic hyperamylasia, and minor bleeding. Carrafiello et al. [33] reported a single case of a potentially resectable pancreatic head adenocarcinoma (4.2 cm) that was treated under computed tomography (CT) guidance with the use of two microwave antennas. They reported a complete ablation, without ablation recurrence during the follow-up period.

These are the only reported cases on the use of MWA in pancreatic lesions. One reason why MWA is not utilized more often for pancreatic lesions/tumors/cysts or cancers is the inability to control the rate of temperature increase. When analyzing its use for liver tumor ablation, an MWA micro-bubble burst occurs at approximately 30–45 s, indicative of temperatures exceeding 100 °C. Based on this, we cannot advocate the use of MWA for treating pancreatic tumors.

High-Intensity Focused Ultrasound

HIFU represents a new and potentially revolutionary technique in the field of ablation. This technique does not require placement of probes or needles to deliver energy to the tumor. This technique works by focusing an intense beam of ultrasound on the tumor to create a thermal effect at the target tissue (Fig. 18.1). HIFU transducers deliver US energy with intensities in the range of 100–10,000 W/cm^2 to the focal target region inducing a "sonication" effect with peak compression pressures of B30 MPa and a peak rarefaction pressures B10 MPa. The acoustic energy is absorbed by the target tissue and transformed to thermal injury-based energy with a result of an increase in the tissue's temperature which then induces coagulative necrosis. The planned temperature threshold of 60 °C is achieved for >10 s to allow for this necrosis. The advantages of HIFU is the precise targeting that may be employed; the beam is precisely focused either under magnetic resonance imaging (MRI) (Fig. 18.2) or real-time US imaging in an attempt to avoid thermal damage to adjunct structures. With the use of MRI, a thermal map of the tissue may also be obtained in the preplanning phase in order to assess the temperatures that will be reached by the surrounding vital structures. Similar targeting using US guidance through the acoustic pathway may be checked before treatment [34].

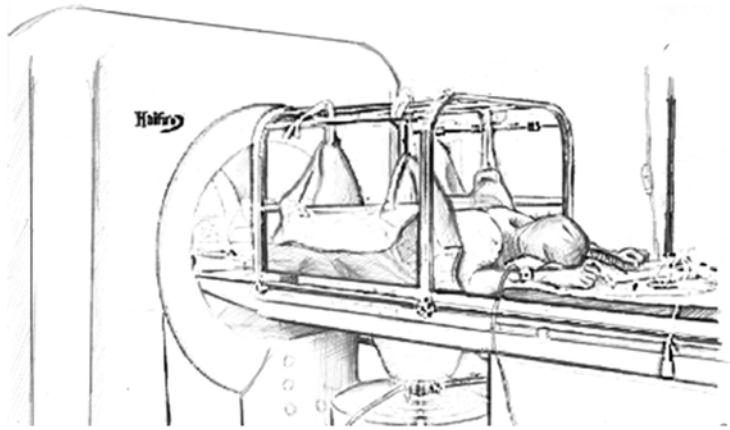

Fig. 18.2 High-intensity focused US ablations are performed through MRI guidance. Typically, the patient is wrapped in a sheath, and then is actually suspended in a prone position above the HIFU ablation probe. A water pack is located between the transducer and the patient. The water pack is basically a degassing water-filled balloon

A recent study evaluated 251 patients with advanced pancreatic cancer (TNM stages II–IV) treated with HIFU. The authors demonstrated that treatment could decrease the size of pancreatic tumors [35] (Table 18.6). In addition, HIFU was effective in 84 % of patients with regard to pain relief. Additional studies from China have confirmed these palliative effects of HIFU [36, 37]. Additional case reports from Europe have demonstrated the safety of HIFU in managing patients with LAPC [38–40]. However, there are no published prospective randomized studies on the use of HIFU with regard to survival and disease recurrence. Thus, additional longer follow-up studies are needed to establish if HIFU is a viable therapeutic option for LAPC beyond pain palliation.

Irreversible Electroporation

IRE represents a new nonthermal injury [41] ablative technique with distinct advantages. It may be used to definitively treat a soft tissue tumor with a decreased risk of thermal damage to vital structures adjacent to pancreatic tissue [13, 15]. The technique uses a series of short (70–90 μs), high-voltage (2250–3000 V) pulses that are applied between two electrodes that are spaced 1.5–2.2 cm apart. This technique increases the permeability of the cell membranes and induces electrolyte disturbances across the cell that lead to cell death via apoptosis [42, 43]. Reversible electroporation has been utilized in basic science labs as a technique that allows for transfer of genetic material or intracellular delivery of drugs [44–46]. The technique of reversible electroporation has a certain threshold to which the electrical energy induces permanent cell membrane porosity leading to irreversible permeabilization [47]. The IRE technique influences only the intracellular environment and not the extracellular matrix, thus allowing for cell repopulation and avoidance of luminal strictures of vital structures [42, 48–50].

Bower et al. [13] reported the first initial use of IRE in a chronic non-tumor-bearing porcine pancreatic model. Six 70–80 kg pigs underwent a midline incision and either 2 or 3 19-gauge monopolar electrodes or one 16-gauge bipolar electrode was placed under ultrasound guidance to avoid mechanical damage and to ensure bracketing of the vital structures. The electrodes were placed within the pancreatic tissue at a distance of 1 mm from the portal vein or the mesenteric artery. Monopolar electrodes were spaced at 1.5

Table 18.6 Studies of high-intensity focused ultrasound in pancreatic ductal adenocarcinoma

Study	*n*	Study	Outcome and survival	Complications
Wang et al. (non-English article)	15	HIFU monotherapy in late stage PDAC	Pain relief: 13/13 (100 %)	Mild abdominal pain (2/15)
Xie et al. (non-English article)	41	HIFU alone + HIFU + gemcitabine in local advanced PDAC	Pain relief: HIFU (66.7 %) HIFU + gemcitabine (76.6 %)	None
Xu et al. (non-English article)	37	HIFU monotherapy in advanced PDAC	Pain relief: 24/30 (80 %)	None
Yuan et al. (non-English article)	40	HIFU monotherapy	Pain relief: 32/40 (80 %)	None
Wu et al.	8	HIFU in advanced PDAC	Median survival: 11.25 months	None
			Pain relief: 8/8	
Xiong et al.	89	HIFU in unresectable PDAC	Median survival: 26.0 months (stage II), 1.2 months (stage III), and 5.4 months (stage IV)	Superficial skin burns (3.4 %), subcutaneous fat sclerosis (6.5), asymptomatic pseudocyst (1.1 %)
Zhao et al.	37	Phase II study of gemcitabine + HIFU in locally advanced PDAC	Overall survival: 12.6 months (95 %) CI: 10.2–15.0 months), pain relief 78.6 %	16.2 % experienced grade 3 or 43 neutropenia, 5.4 % developed grade 3 thrombocytopenia, 8 % had nausea vomiting
Orsi et al.	6	HIFU in unresectable PDAC	Pain relief: 6/6 (100 %)	Portal vein thrombosis (1/6)
Sung et al.	46	Stage III or IV PDAC	Median survival: 12.4 months. Overall survival at 12 months was 30.4 %	Minor complications (abdominal pain, fever, and nausea): 57.1% (28/29). Major complications (pancreaticoduodenal fistula, gastric ulcer, or skin burns): 10.2 % (5/49)
Wang et al.	40	Advanced PDAC	Median overall survival: 10 months (stage III) and 6 months (stage IV) Pain relief: 35//40 (87.5 %)	None
Lee et al.	12	HIFU monotherapy in unresectable PDAC (33/12 received chemotherapy)	Median overall survival for those receiving HIFU alone (9/12 pts): 10.3 months	Pancreatitis 1/12
Li et al.	25	Unresectable PDAC	Median overall survival: 10 months. 42 % survived more than 1 year, performance status and pain levels improved: 23/25	First degree skin burn: 12 %
				Mortality: 0 %
Wang et al.	224	Advanced PDAC	Not reported	Abdominal distension, anorexia, and nausea: 10/224 (4.5 %) Asymptomatic vertebral injury: 2/224
Gao et al.	39	Locally advanced PDAC	Pain relief: 79.5 %	None
			Median overall survival: 11 months. 30.8 % survived more than 1 year	

HIFU high-intensity focused ultrasound, *PDAC* pancreatic ductal adenocarcinoma

Table 18.7 Current reports with overall survival with the use of IRE in Locally Advanced Pancreatic Cancer

Author, year	Ablation success reported and defined	Overall survival (Y/N) median	Local recurrence	Mortality	Complications
Strobel, 2013	–	16.4 months	59 %	0.9 %	Pancreatic fistula, wound infections, burns, UTI, intra-abdominal abscess
Martin, 2012	54 patients IRE successfully	20 months	(15/54) 28 %	2 %	None
Martin, 2012	27 patients 100 % success	All lived to 90-day post-op scan	0 % at 90 days	(1/27) 3.7 %	Hematologic, Ileus, bile leak, portal vein thrombosis, deep venous thrombosis, pulmonary, renal failure, wound infection
Dunki-Jacobs, 2014	65 patients 100 % success	The median local disease-free survival was 5.5 months in patients who had recurrence compared with 12.6 months in patients who did not recur ($p=0.03$)	(17/65) 26 %	–	Ileus, bile leak, portal vein thrombosis, pulmonary, renal failure, wound infection, liver insufficiency, dehydration
Narayanan 2013	14 patients treated percutaneously	Median DFS 6.7 (0.7–12.7)	Not reported	0 % at 30 days	Pancreatitis and Pneumothorax

and 2 cm apart. The electroporation generator was the NanoKnife system (AngioDynamics, Queensbury, NY), which utilized an energy output of a maximum of 3000 V and maximum current of 50 amps. The goal of treatment is to deliver enough pulses (range 110–220) in groups of 10 in order to see a change in resistance of the target tissue [51]. All animals tolerated the IRE procedure of the pancreas, and the animals had a transient (peak at 48 h) increase in pancreatic enzymes (normalized at 72 h in most animals). The animals were survived to 72 h, 7 days, and 14 days after the procedure. Pathology demonstrated complete electroporation with nonthermal injury-induced necrosis of pancreatic cells adjacent to vascular structures. There was no evidence of thermal injury to the vessels or bile ducts. The authors concluded from this preliminary study that IRE might be used in the ablation of pancreatic tissue without significant risk of pancreatitis or vascular thrombosis.

The initial clinical use of IRE was reported by Martin et al. Twenty-seven patients (13 men, 14 women) with pancreas tumors were treated with IRE [52] (Table 18.7). Eight patients underwent margin accentuation with IRE in combination with left-sided resection ($N=4$) or pancreatic head resection ($n=4$). Nineteen patients had in situ IRE. All patients underwent successful IRE, with intraoperative imaging confirming effective delivery of therapy. All 27 patients demonstrated nonclinically relevant elevation of their amylase and lipase, which peaked at 48 h and returned to normal at 72 h post-procedure. There was a 90-day mortality. No patient demonstrated evidence of clinical pancreatitis or fistula formation. In patients that had in situ ablation, 90-day follow-up demonstrated 100 % ablation. The authors concluded that IRE ablation of locally advanced pancreas tumors was safe and feasible for treating unresectable, locally advanced disease.

Martin et al. reported on a larger study of 54 patients who underwent combination of chemotherapy and chemoradiation therapy with consolidative IRE in comparison to a control group of chemotherapy/chemo-radiation therapy for LAPC [53]. All patients were confirmed to have Stage 3 LAPC based on staging CT and/or MRI due to encasement of the superior mesenteric artery, celiac axis, or long segment occlusion of the SMV/PV. IRE was performed through an open midline incision or in a laparoscopic fashion. After a median follow-up time of 15 months, 15 of the 54 patients appeared to have local disease recurrence. The adverse events that were IRE related included two cases of bile leakage and two cases of duodenal perforation. The 90-day mortality in the IRE patients was 2 %. Comparison of IRE patients to the standard therapy demonstrated improvement in local progression free survival (14 months vs. 6 months, $p=0.01$), distant progression free survival (15 months vs. 9 months, $p=0.02$), and overall survival (20 months vs. 13 months, $p=0.03$). The investigators concluded that IRE as a consolidative therapy for locally advanced pancreatic tumors remained feasible and safe. In the appropriate patient who has undergone standard induction therapy for a minimum of 4 months, IRE can achieve greater local palliation and potential improved overall survival when compared to standard chemoradiation–chemotherapy treatments.

Another option to deliver IRE is the use of a percutaneous access approach. Narayanan et al. [54] performed a study on 14 patients who received CT-guided percutaneous treatment with IRE for locally advanced pancreatic cancer. The indications for treatment were downstaging of the locally advanced cancer, control of local recurrence after previous Whipple procedure, and/or intolerance to systemic chemotherapy. All patients had received previous cycles of chemotherapy and 10 of 14 also received previous radiation therapy. The median tumor size treated was 3.3 cm (range 2.5–7). In six cases, the tumor was located in the pancreatic head; in seven cases, it was located in the body, and in one case it was located in the uncinate process. In three cases, small-volume metastatic disease was present, whereas patients with extensive metastatic disease were not included in the study. No severe complications occurred after the procedure. Complications included pneumothorax, a small subcutaneous hematoma, and self-limiting pancreatitis. There were four deaths during the course of the follow-up; however, no deaths were attributed to the procedure. Three other patients with intolerance to chemotherapy showed stable disease and did not require any further treatment. The median overall survival was reported as 6 months. With these results, the investigators concluded that patients with metastatic disease do not appear to benefit from IRE and that patients with extensive varices need to be excluded, from a percutaneous approach thus indicating that a safe CT "window" is not enough for percutaneous IRE of locally advanced pancreatic cancer.

The recommendations to (1) avoid treating patients with metastatic disease and (2) avoid incomplete ablation of tumors cannot be overstated. A recent report from Philps et al. created the first ever heterotopic murine model by inoculating BALB/c nude mice in the hind limb with a subcutaneous injection of Panc-1 cells, an immortalized human pancreatic adenocarcinoma cell line [55]. Tumors were allowed to grow from 0.75 to 1.5 cm and then treated with the goal of complete ablation or partial ablation using standard IRE settings. Animals were recovered and survived for 2 days ($n=6$), 7 days ($n=6$), 14 days ($n=6$), 21 days ($n=6$), 30 days ($n=8$), and 60 days ($n=8$). All 40 animals/tumors underwent successful IRE under general anesthesia with muscle paralysis. The mean tumor volume of the animals undergoing ablation was 1447.6 $mm^3 \pm 884$). Histologically, in the 14-, 21-, 30-, and 60-day survival groups the entire tumor was nonviable, with a persistent tumor nodule completely replaced with fibrosis. In the group treated with partial ablation, incomplete electroporation/recurrences ($N=10$ animals) were seen. 66 % had confluent tumors and this was a significant predictor of recurrence ($p<0.001$). Recurrent tumors were also significantly larger (mean 4578 $mm^3 \pm$ SD 877 vs. completed electroporated tumors 925.8 ± 277, $p<0.001$). Recurrent tumors had a steeper growth

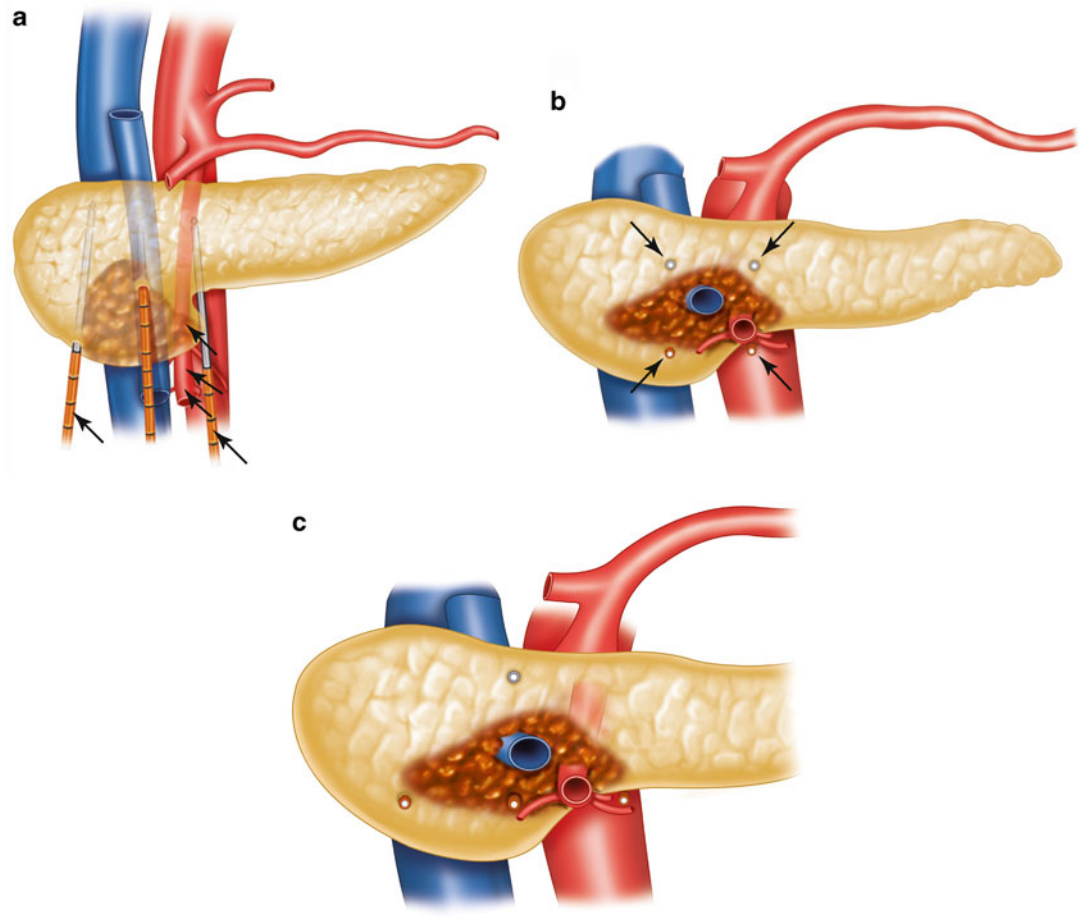

Fig. 18.3 (**a**) Coronal plane of standard 4-probe technique with SMA encasement. Care should be taken so that the needles are not placed past the extent of tumor involvement, thus preventing injury to aorta. (**b**) Axial plane of classical 4 probe—box technique for a locally advanced pancreatic head tumor with SMA and SMV encasement with 4 probes bracketing the tumor and the SMA with max probe exposure of 1 cm. (**c**) Axial image of LAPC of the pancreatic head with a triangle IRE probe configuration, which is sometimes required because of the posterior/retroperitoneal extension is wider than the anterior apex of the tumor

curve (Slope = 0.73) compared with primary tumors (0.60, $p = 0.02$). Recurrent tumors also had a significantly higher percentage of EpCAM expression, suggestive of stem cell activation. The authors concluded that tumors that recur after incomplete electroporation demonstrate a biologically aggressive tumor that could be more resistant to standard chemotherapy. Clinical correlation of this data is limited, but should be considered when IRE of pancreatic cancer is planned.

The established technique for IRE of LAPC has been well published and described. A recent report from Martin et al. reported on the optimal technique for both the LAPC of the pancreatic head and LAPC of the pancreatic neck/body [56, 57]. A representative case would be a patient who presents a LAPC of the pancreatic head who has been treated with induction chemotherapy, who now has a mass of <3.5 cm in size with clear vascular involvement (Fig. 18.3). Given the size of the tumor, at least four needles are placed in a bracketing fashion, covering the entire tumor and the vital structures, which in this case would include the SMA, SMV, and the bile duct.

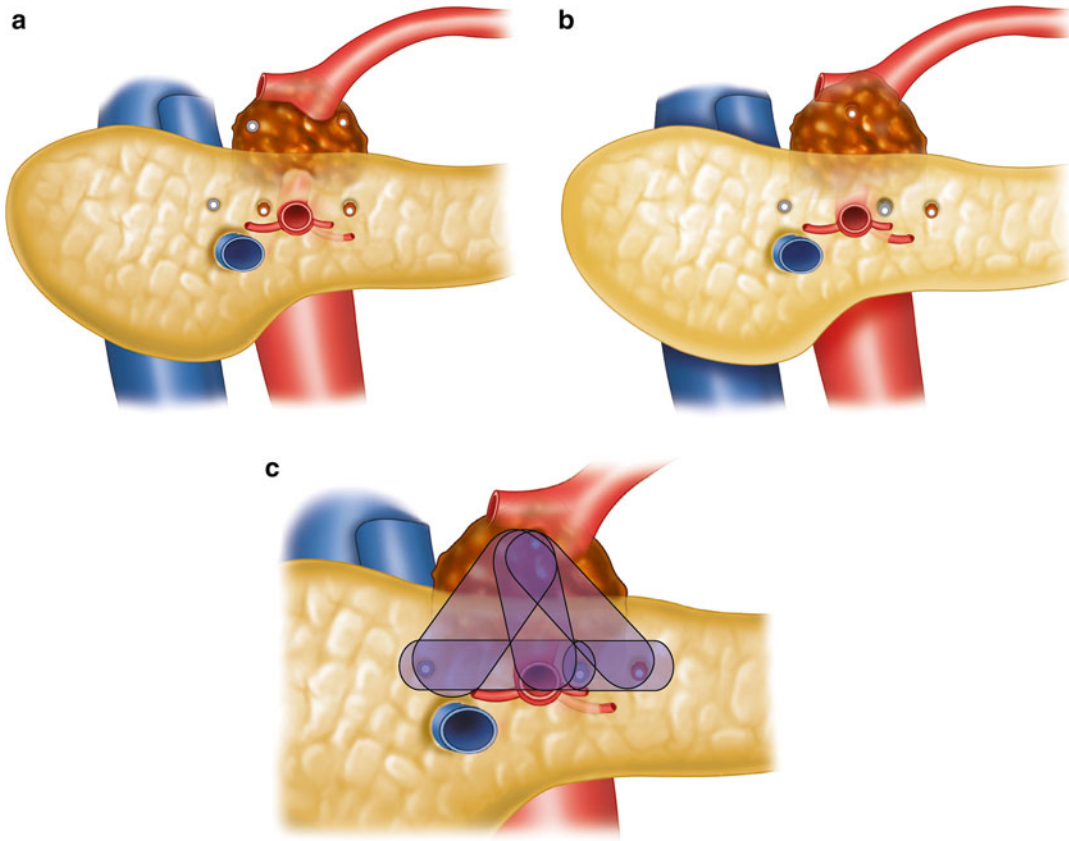

Fig. 18.4 (**a**) Axial plane of classical four probe—box technique for a locally advanced pancreatic mid-body tumor with just celiac encasement and SMA involvement with four probes (*single arrow head*) bracketing the tumor and the celiac axis with max probe exposure of 1 cm; (**b**) sagittal plane of this same four probe technique; (**c**) example of energy delivery that occurs between probes for a total of six probes with IRE energy delivered. *IRE* irreversible electroporation, *SMA*

A similar algorithm can be utilized with LAPC of the neck, which again should be extensively staged and then treated with initial induction chemotherapy. After appropriate selection the needle placement again should be in a bracketed fashion to cover the entire tumor and the vital structures that the tumor invades (Fig. 18.4). After optimal needle placement, with precise spacing [58], the energy is delivered between the probes in a sequential fashion until a change in resistance is seen [51].

Conclusion

LAPC remains a distinct disease with a clearly different biology than Stage 4 pancreatic cancer. Demands to separate these two distinct diseases is required to better risk stratify and care for this subset of patients. Surgical evaluation at the time of diagnosis in conjunction with high quality imaging is required, in conjunction with repeated evaluation at 2–3 month intervals while on induction chemotherapy. Only after the biology of the disease is determined—i.e., lack of progression within the first 4–6 months—should any type of local therapy be considered. Currently, with the inability to control the distribution of the thermal-based injury—RFA and MWA have no role in the management, care, or palliation of patients with LAPC. Attempts to extrapolate what is know about RFA and MWA in the liver with regard to universally recognized and intentionally radical "safety halo" of necrosis is achieved around the target lesion does not translate into the pancreas.

The inability to obtain that "safe halo" without running excessive risks of perioperative complications is the most important limitation of any thermal ablative technique in the pancreas. HIFU has potential given that it can eradicate all disease in an LAPC without injuring surrounding vascular structures. IRE can have a clear role in the local control of Stage 3 and borderline pancreatic adenocarcinoma **IF AND ONLY IF** used responsibly with the highest technical quality and extensive knowledge of IRE clinical endpoints and LAPC. Significant limitations remain in 2015 with IRE: The capital generator expense and probe expense is outside of the norm when compared to other thermal injury-based devices. Intra-procedural targeting is limited at this time and represents a limitation to the wider expansion of this technique. Lastly, the limited ability to confirm IRE success and IRE recurrence with the current imaging modalities will require expansion into higher quality molecular imaging. Thus in conclusion, local consolidative therapy for LAPC can be effective in local disease control when performed in collaboration with a multidisciplinary team and appropriate sequencing of all three therapies—chemotherapy, radiation therapy, and IRE.

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19 Surgical Approach to Borderline Resectable Tumors of the Left Pancreas

Nicholas Spinelli and William Hawkins

Introduction

Resections of the pancreas typically involve removal of either the pancreatic head or varying portions of the pancreatic body and tail depending on the actual location of the tumor. The line of transection during a typical pancreaticoduodenectomy is constant in most cases and is that region of parenchyma directly overlying the SMV/portal vein, often called the pancreatic neck. Occasionally, that line of transection will move to the patient's left should the tumor extend out of the pancreatic head. However, from a surgical anatomy standpoint the pancreatic head is defined as all of the pancreatic tissue lying to the right of the SMV/portal vein. Similarly, the *left pancreas* is defined as all of the pancreatic tissue lying to the left of the SMV/portal vein. It contains both the body and tail of the pancreas as is commonly depicted in anatomy texts. Traditionally, the line of parenchymal transection for tumors of the left pancreas is not always constant and can move leftward from the SMV/portal vein with more distal locations of disease (i.e., those located in the tail.) Thus, a distal pancreatectomy is a more nebulously defined concept in comparison to the typical Whipple procedure when referring to the actual location of parenchymal transection. In this chapter we will be discussing what we believe is the optimal approach to the oncologic resection of the left side of the pancreas. We advocate for a modular approach employing a constant transection line in typical resections of malignant tumors of the left pancreas. That line is at the SMV/portal vein. Thus, the entire left pancreas is removed regardless of the tumor's location within the body or tail. Occasionally, the pancreas will require division at the union of the head and neck in order achieve a negative margin.

Initial Evaluation of a Left Pancreas Mass

Tumors of the left pancreas are often identified at a more advanced stage in comparison to those lesions located in the pancreatic head. The reason for this lies in the fact that pancreatic head lesions often present with painless jaundice as tumor encroaches on the distal common bile duct. This "early warning sign" does not exist with left-sided tumors. Often times, left-sided lesions are identified on diagnostic imaging when the mass becomes large enough to produce abdominal discomfort or early satiety. Some lesions, however, are fortuitously identified on imaging performed for other reasons. Incidental tumors are more

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likely to be early stage and therefore surgically resectable. As a result, incidental tumors of the distal pancreas are more likely to be cured than symptomatic tumors.

A pancreatic ductal adenocarcinoma should lead the differential diagnosis for any solid mass located in the left pancreas, particularly in those patients over the age of 40 years. However, other considerations include neuroendocrine carcinoma, metastatic neoplasms (renal cell carcinoma in particular), pancreatoblastoma, acinar cell carcinoma, solid pseudopapillary neoplasm, pancreatic lymphoma, chronic or autoimmune pancreatitis, and the rare mesenchymal tumor.

The initial evaluation of a potential pancreas cancer is discussed elsewhere in this volume, and a complete discussion of this topic is beyond the scope of this chapter. However, it is important to note that further workup and treatment of a left pancreas mass is typically based on axial imaging (i.e., pancreas protocol CT scan) just as it is for a lesion in the head of the pancreas. Metastatic disease in the liver, peritoneum, or lymph nodes outside of the field of resection is assessed with abdominal imaging. Extra-abdominal stage IV disease may be further ruled out with chest imaging. Assuming local disease, the primary lesion's resectability is assessed based on vascular involvement and further treatment is discussed at a multidisciplinary conference with representation from surgery, interventional gastroenterology, radiology, medical oncology, and radiation oncology. Please see Chap. 1 for a complete discussion on resectability.

Multimodality therapy is an important concept in the contemporary management of cancer and is discussed extensively in section III as related to pancreas cancer. Therefore, multidisciplinary review of cancers involving the left pancreas cannot be overemphasized. Determination of resectability is not always straightforward as tumor contact with the vasculature can be quite difficult to determine especially when contact appears more as perivascular fat stranding than as definite solid abutment. For those lesions that are deemed borderline or locally unresectable by consensus, we advocate for systemic chemotherapy followed by imaging reassessment at our institution. If the mass proves to be resectable on repeat imaging, surgical exploration is warranted. If the patient's response to chemotherapy is minimal or nonexistent, we typically proceed with chemoradiation followed by reassessment. Every effort is made to achieve resectability by imaging before proceeding to the operating room with patients who initially present with borderline/locally advanced unresectable tumors.

Before chemotherapy is initiated, the diagnosis of adenocarcinoma is generally confirmed via tissue diagnosis and assessment of serum tumor markers. This can be accomplished by fine needle aspiration either by CT guidance or via endoscopic ultrasound (EUS). It is our preference to employ EUS-guided biopsy. Although definitive tissue diagnosis is necessary prior to the start of chemotherapy, we do not require a biopsy in the clearly resectable patient with a left pancreas mass that is clinically suspicious for pancreatic adenocarcinoma.

Surgical Management of Left Pancreas Cancers

Our preferred approach to the extirpation of an adenocarcinoma of the left pancreas is a modification of the traditional left pancreatectomy which we call a *R*adical *A*ntegrade *M*odular *P*ancreato*S*plenectomy (RAMPS). The RAMPS procedure is a relatively recent technical modification of the more standard retrograde distal pancreatectomy with splenectomy. Two problems with the traditional approach to left pancreas cancers have been identified. One is a potentially inadequate posterior resection margin. The other is a limited ability to capture all N1 lymph nodes in the field of resection. The RAMPS procedure is an attempt to improve upon these shortcomings so that better patient outcomes may be realized [1].

There are two groups of lymph nodes that drain the body and tail of the pancreas (see Fig. 19.1). There are lymphatic vessels that course along the superior and inferior borders of the pancreas. Depending on the cancer's exact location, it will drain along these lymphatics either leftward

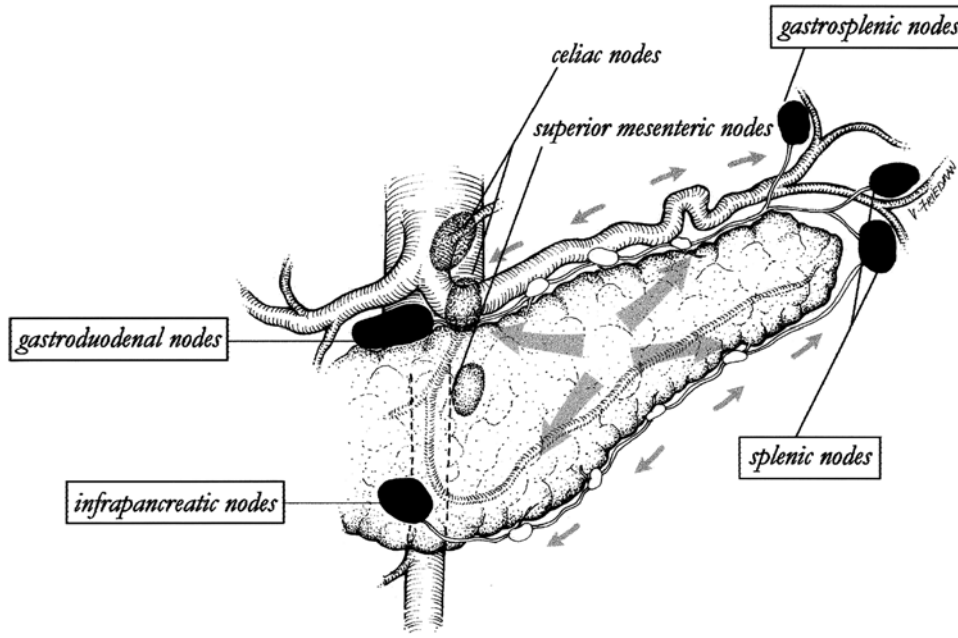

Fig. 19.1 Lymphatic drainage. of the left pancreas. The ring of nodes consists of the lymph nodes located at the superior and inferior border of the pancreas as well as the gastrosplenic, splenic, gastroduodenal, and infrapancreatic nodes. The celiac and superior mesenteric lymph nodes may also receive direct drainage without having received drainage from any of the ring nodes. Therefore, they are oncologically important in resection of cancers of the left pancreas. (*Reproduced with permission from* [1])

toward the splenic nodes and gastrosplenic nodes or rightward toward the gastroduodenal and infrapancreatic nodes. These four lymph node groups form one of the two groups of lymph nodes draining the left pancreas and are known as the ring of nodes. The second group of lymph nodes consists of anterior aortic lymph nodes and they are anatomically related to the celiac and superior mesenteric arteries. This group of lymph nodes can be classified as N2 nodes. However, as detailed by O'Morchoe [2], there isn't always linear, sequential drainage of lymphatic fluid from the cancer, to the first group of nodes, and then on to the second group of nodes. This means that lymphatic drainage from the cancer can enter the anterior aortic nodes directly without having seen any of the nodes on the ring. Therefore, these lymph nodes technically behave as N1 nodes for tumors of the left pancreas. The RAMPS procedure is designed to specifically remove the ring of nodes as well as the second group of lymph nodes along the celiac axis and the left aspect of the superior mesenteric artery.

The operation generally commences with a staging laparoscopy to evaluate for obvious metastatic disease on the liver surface or peritoneum. Identification of such metastatic disease would obviate the need to resect the cancer. Assuming that the patient is free of metastatic disease on staging laparoscopy, the abdomen can be entered in one of two ways. A midline incision is perhaps the easiest method of entry and provides adequate exposure in the majority of patients. Occasionally a "Mercedes Benz" incision is required. This entails a left subcostal incision that is extended to the right subcostal region with the addition of a vertical incision at the midline. Having entered the abdomen, the peritoneal cavity is once again explored for obvious metastatic disease. Particular attention is paid to the root of the mesentery as seen when elevating the transverse colon toward the patient's head.

The lesser sac is entered by taking the greater omentum off of the colon. This involves division of the avascular embryologic fusion plane between the greater omentum and the transverse colon. Alternatively, the lesser sac can be entered by simply dividing the greater omentum just outside of the gastroepiploic arcade preserving blood flow to the greater curvature of the stomach. The short gastric vessels will require division and this can be fully accomplished at this stage of the operation or completed with mobilization of the spleen. The RAMPS procedure then starts with early division of the neck of the pancreas. This is performed by first identifying the SMV at the inferior border of the pancreas with or without division of the right gastroepiploic vein but taking care not to injure the middle colic vein if possible. Before the anterior portal vein is identified a wide Kocher maneuver is performed and the hepatic flexure is taken down in an effort to expose the anterior IVC and the proximal left renal vein. This structure will serve as the starting point of the posterior extent of the resection plane. The anterior surface of the portal vein is now identified at the superior border of the pancreas by rightward retraction of the gastroduodenal artery after having mobilized the lymph nodes along the left side of the proper hepatic artery and portal vein as well as the lymph nodes associated with the common hepatic artery. The anterior surface of the portal vein is then found in the space just to the left of the GDA and inferior to the common hepatic artery. The retropancreatic tunnel is developed at this point and the pancreatic neck is divided. The pancreas is typically stapled with mesh, as this has shown promising results in significantly decreasing the rate of pancreatic occlusion failure in our single institution study [3]. Early division of the pancreatic neck is in stark contrast to the more traditional retrograde method where the pancreatic neck is divided lastly. However, this maneuver is important in the RAMPS procedure because it allows for an adequate celiac lymph node dissection, which is necessary if all N1 nodes are to be removed.

The celiac lymph node dissection is performed next after having divided the neck of the pancreas. As the fat and lymph nodes anterior to the common hepatic artery are dissected and carried medially, the celiac trunk will come into view. The left gastric artery is identified and its associated lymph nodes are swept inferiorly as the origin of the splenic artery is approached. Note that the left gastric artery can be sacrificed making the celiac lymph node dissection easier; however, this is certainly contraindicated in the presence of a replaced left hepatic artery arising from the left gastric artery. Once the origin of the splenic artery is identified, it is divided and ligated. Following this, the splenic vein is circumferentially dissected, divided, and ligated. Although it is ideal from a splenic congestion standpoint to divide the splenic artery before taking the vein, occasionally, patient anatomy will dictate that it is technically easier to divide the splenic vein before the artery.

Having completed the celiac lymph node dissection, attention is now turned towards clearing lymphatic tissue from the left side of the SMA as well as the small span of anterior aorta located between the celiac trunk and SMA. This is accomplished by orienting the plane of dissection sagittally towards the patient's spine with the goal of being able to visualize the origins of both the celiac trunk and SMA from the left side of the aorta.

The conduct of the final portion of the RAMPS procedure is dictated by the cancer's proximity to the left adrenal gland and determined preoperatively based on imaging. The more commonly indicated anterior RAMPS procedure is done for tumors that are medially located where there is no involvement with the left adrenal gland. However, should the tumor's location be lateral and abutting the left adrenal gland it is prudent to proceed with a posterior RAMPS procedure (see Fig. 19.2).

Anterior RAMPS: The previously identified left renal vein is identified and becomes the posterior plane of dissection at the most medial extent of the specimen. The final extirpation now proceeds in a medial to lateral fashion (i.e., antegrade). The left adrenal vein is next identified and the dissection stays just anterior to its surface as well as the left adrenal gland itself. As the dissection proceeds more laterally, the peritoneum at

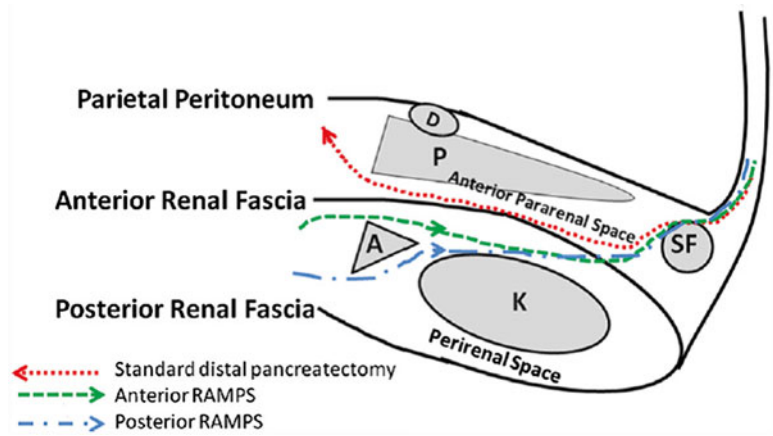

Fig. 19.2 Planes of posterior margin and direction of dissection in the different types of left pancreatectomies including the two RAMPS procedures. *A* left adrenal gland, *D* duodenum, *K* left kidney, *P* pancreas, *SF* splenic flexure of colon. (*Reproduced with permission from* [4])

the superior and inferior borders of the pancreas are freed. This entails division and ligation of the inferior mesenteric vein. Posteriorly, the anterior renal fascia is generally removed from the superior pole of the kidney as the pancreas is elevated out of the retroperitoneum. After division of the lienorenal attachments, the specimen is removed from the abdomen (see Fig. 19.3).

Posterior RAMPS: The dissection is carried down the left side of the aorta onto the diaphragm. The left renal vein forms the inferior border of the dissection at the medial extent of the specimen. This is similar to the previously described anterior RAMPS. However, as the dissection proceeds antegrade, the correct plane lies posterior to the adrenal gland on the retroperitoneal muscle layer. This step involves ligation and division of the left adrenal vein so that the adrenal gland can be removed with the specimen. The attachments at the superior and inferior borders of the pancreas are divided as well as the IMV, just as in the anterior RAMPS. Also, the anterior renal fascia is always taken in a posterior RAMPS procedure as the pancreas is mobilized laterally. Therefore, the final specimen will include the left pancreas, left adrenal gland, and spleen en bloc (see Fig. 19.4).

Left pancreas cancers can grow to large sizes before their detection and thus may present with local invasion into surrounding structures other than the left adrenal gland. Those structures may include the stomach, left kidney, transverse mesocolon, colon, duodenum, and diaphragm. Local invasion of any of these structures does not preclude resection of the cancer as long as the involved structures can be completely removed en bloc with the specimen using standard resection techniques. Occasionally, it may be necessary to extend the left pancreatectomy to the right depending on the actual location of the mass. This is particularly true if there is invasion of the portal vein/superior mesenteric vein, where venous reconstruction may be necessary to completely extirpate the tumor. Figure 19.5 depicts a CT scan of a patient with venous involvement from a left-sided pancreas cancer where this technique may be necessary. It should be noted that while venous resection/reconstruction is generally accepted for complete extirpation of pancreatic cancer, similar consensus does not exist if SMA reconstruction is necessary to achieve negative margins. SMA resection has been found to increase morbidity and negatively impact survival [5].

Shoup et al. [6] conducted a retrospective analysis of patients undergoing extended resection for adenocarcinoma of the left pancreas (defined as resection of the left pancreas en bloc with contiguously involved superior mesenteric vein/portal vein and/or organs. Their goal was to determine if extended resection is justified based on their long-term survival data. Distal pancreatectomy was performed in 57 patients where an extended resection was necessary in 22 patients.

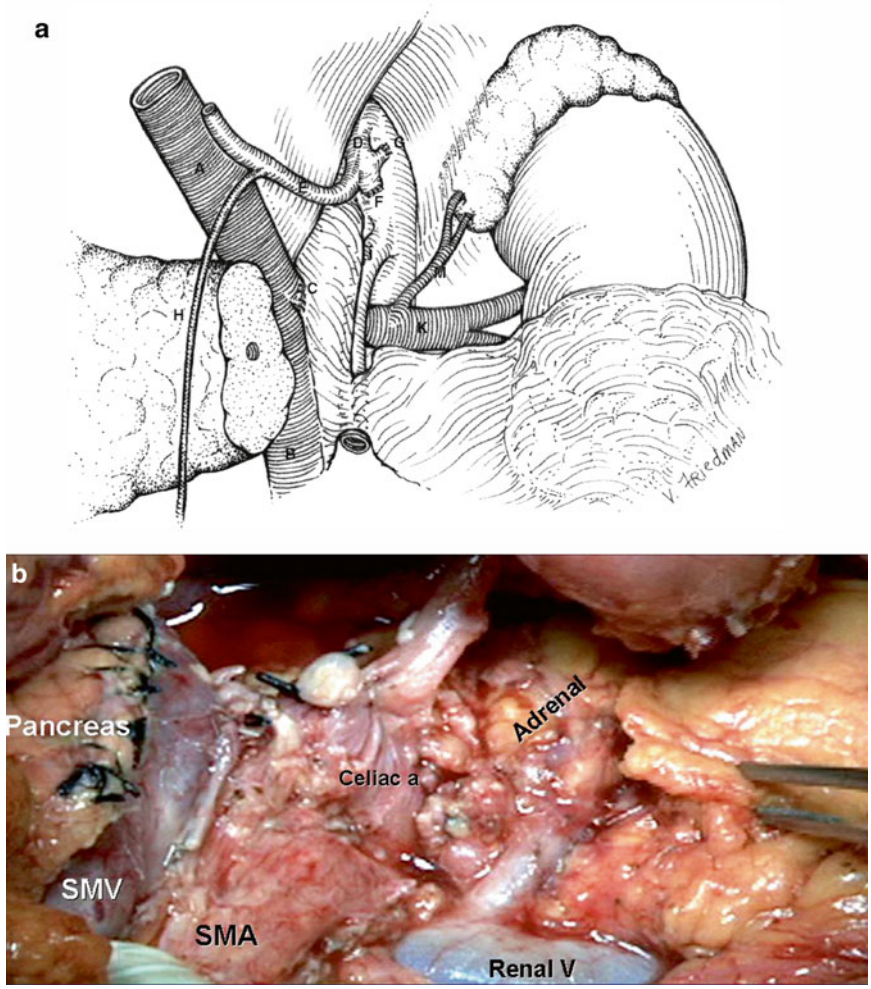

Fig. 19.3 (**a**) Drawing of the operative field at the conclusion of an anterior RAMPS procedure. (*a*) Portal vein, (*b*) superior mesenteric vein, (*c*) stump of the splenic vein, (*d*) celiac artery, (*e*) common hepatic artery, (*f*) stump of the splenic artery, (*g*) stump of the left gastric artery, (*h*) gastroduodenal artery, (*j*) superior mesenteric artery, (*k*) left renal vein, (*m*) left adrenal vein. (**b**) Labelled intraoperative photograph at the conclusion of an anterior RAMPS procedure. (*Both figures reproduced with permission from* [1])

Fourteen extended resection patients had contiguous organ involvement while eight patients had portal venous involvement. Multivariate analysis suggested a significantly longer length of stay ($P=0.02$), higher blood loss ($P=0.02$), and increased transfusion requirement ($P=0.01$) in the extended resection patients in comparison to those who did not require an extended resection (standard resection patients). However, there was not a statistically significant difference ($P=0.80$) in median disease-specific survival between extended resection patients (9 months) and standard resection patients (16 months). Actual 5- and 10-year disease-specific survival was 22 % and 18 %, respectively, for extended resection patients and 8 % and 8 %, respectively, for standard resection patients. Based on similar long-term survival data the authors concluded that extended surgery to resect either contiguous organs or involved portal vein in an effort to achieve an R0 resection is acceptable and should be performed.

A similar retrospective analysis was conducted by Christein et al. [7]. The authors studied

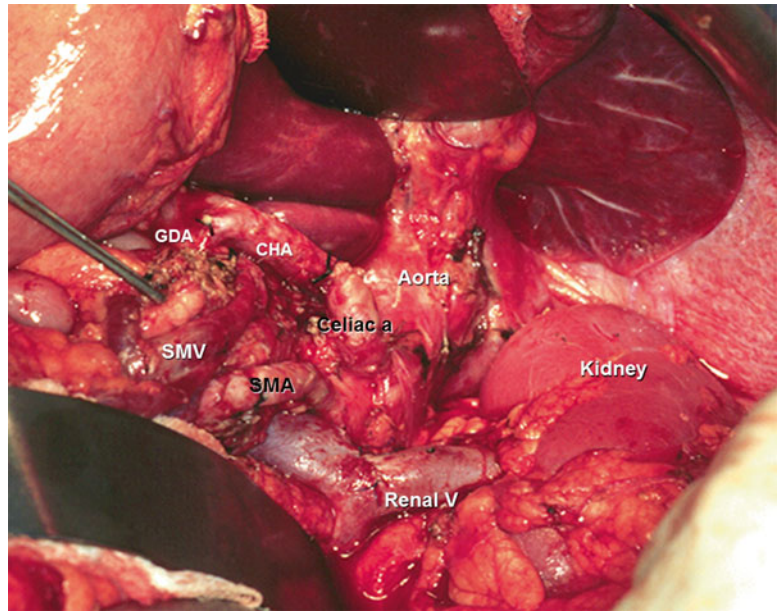

Fig. 19.4 Labelled intraoperative photograph at the conclusion of a posterior RAMPS procedure. (*Reproduced with permission from* [1])

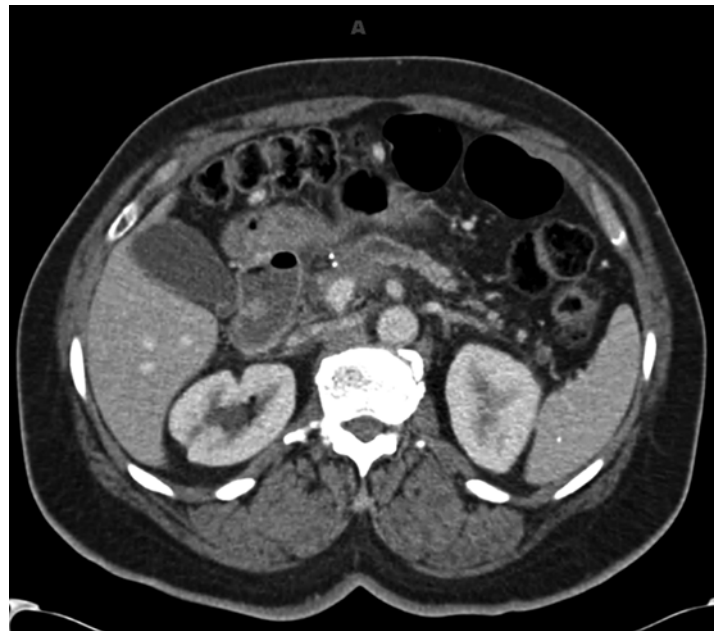

Fig. 19.5 An axial slice from a CT scan of a patient with a hypoattenuating left-sided pancreatic cancer that is invading the portal vein

survival in three subtypes of adenocarcinoma located in the left pancreas, which included typical ductal adenocarcinoma, mucinous cystadenocarcinoma, and adenocarcinoma associated with intraductal papillary mucinous neoplasms. Ninety-three patients had undergone distal pancreatectomy—33 of those patients required an en bloc resection, including one or more adjacent organs. Patients undergoing en bloc resection of contiguous structures had statistically significant more complications ($P=0.03$), higher blood loss ($P=0.16$), and required more blood transfusions ($P=0.25$) than those patients not receiving en bloc resections. Also, the intensive care unit

admission rate was significantly higher in the en bloc resection group ($P=0.004$) as well as the R1 resection rate ($P=0.04$). Median survival in en bloc resection patients was 14.1 months and 16.2 months in the standard resection patients. This difference in survival was not statistically significant ($P=0.88$). Therefore, the authors concluded that although distal pancreatectomy with en bloc resection of contiguous organs results in a higher complication rate, survival is not significantly affected and extended resections are indicated.

Evidence Supporting Use of the RAMPS Procedure

As mentioned above, the RAMPS procedure was designed to address two problems that were identified with the traditional distal pancreatectomy and splenectomy performed in the left to right manner. The first problem is the high tangential margin rate. The second problem is the low lymph node count. Strasberg et al. [8] reported on the Washington University experience with the RAMPS procedure after having designed and introduced it into their technical armamentarium in 1999. Using a prospective database, the authors identified 15 patients who had undergone an anterior RAMPS and 8 patients who had undergone a posterior RAMPS. These cases were associated with a 52 % complication rate but no perioperative deaths. Ninety-one percent of patients had negative tangential margins despite 78 % of these cancers invading through the pancreatic capsule. The median number of lymph nodes resected with the specimen was 15. The technical modifications involved in the conduct of the RAMPS procedure led to a 21-month median survival and a 26 % overall 5-year survival. This survival data is similar to that of the Whipple procedure. This led the authors to conclude that a high rate of negative tangential margins can be obtained with the RAMPS procedure and that the operation is associated with acceptable survival statistics. This has led the Washington University group to adopt the RAMPS procedure as their standard approach to left pancreas cancers.

The RAMPS procedure has been additionally studied by Chang et al. [9]. A negative tangential margin rate of 91.7 % was reported as well as an 18-month median survival. This led the authors to conclude that the RAMPS procedure is an acceptable method of obtaining negative tangential margins in cancers of the left pancreas.

Having proven the feasibility of the RAMPS procedure in 2007, the Washington University group presented long-term data on the procedure in 2012 [10]. Forty-seven RAMPS patients were identified in their prospective database. Thirty-two patients had undergone an anterior RAMPS while 15 had undergone a posterior RAMPS. There were no perioperative deaths. Negative tangential margins were noted in 89 % of the specimens contributing to a 26-month median survival and 35.5 % overall 5-year survival (see Fig. 19.6).

Comparing RAMPS to Traditional Approach to Left Pancreas Tumors

Latorre et al. compared standard retrograde pancreatosplenectomy with the RAMPS procedure in a retrospective review of 25 patients at one hospital in Rome, Italy [11]. Eight patients underwent RAMPS as defined by Strasberg et al. in 2003 and 17 underwent standard retrograde pancreatosplenectomy. The authors found that there were no differences in estimated blood loss, intraoperative blood transfusions, postoperative morbidity and mortality, and hospital stay between the two groups. Furthermore, the positive margin rate was not significant between the two groups. However, it is important to note that two patients had a positive *tangential* margin, both of whom had received the standard retrograde pancreatosplenectomy. Also, the number of harvested lymph nodes differed statistically between the two groups with the RAMPS procedure yielding a greater number of nodes for pathologic analysis. Regarding actuarial 5-year overall survival, there was no statistical difference between standard retrograde pancreatosplenectomy patients and RAMPS patients. The authors concluded that the RAMPS

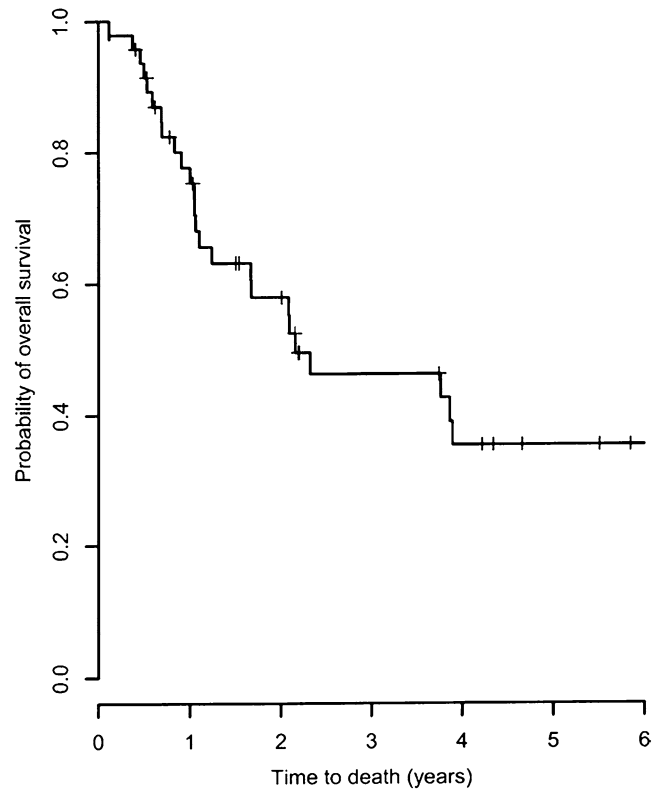

Fig. 19.6 Overall survival results of RAMPS procedure. The curve is censored at 6 years, which is the time point beyond which fewer than 10 % of patients have been followed. Hatch marks indicate censored patients within the 6-year follow-up period. (*Reproduced with permission from* [10])

procedure achieved better tangential margins but there was no difference in the overall 5-year survival between the two surgical groups in this small study.

Trottman et al. compared the standard distal pancreatectomy and splenectomy with the RAMPS procedure looking specifically at the number of lymph nodes removed [12]. The authors retrospectively reviewed 20 patients who had undergone a standard resection and six patients who had undergone a RAMPS procedure. Not all cases were performed for adenocarcinoma preventing the authors from conducting a meaningful analysis about margin status and cancer survival. They did look at lymph node retrieval and learned that there was a significantly larger number of lymph nodes harvested from a RAMPS procedure compared to the traditional approach to distal pancreatectomy and splenectomy—11.2 vs. 4.3 (P = 0.03). The authors recommended the RAMPS procedure over retrograde distal pancreatectomy/splenectomy when lymph node count is essential for cancer staging and prognosis (i.e., ductal adenocarcinoma of the body and tail).

Park et al. examined their experience with the RAMPS procedure comparing it to the traditional distal pancreatosplenectomy [13]. The authors retrospectively reviewed 92 patients who underwent surgery for adenocarcinoma of the body and tail of the pancreas in Korea. Thirty-eight patients received the RAMPS procedure while 54 patients underwent conventional distal pancreatosplenectomy. A statistically larger number of lymph nodes were retrieved in the RAMPS group but there was no statistical difference in the R0 resection rate. The RAMPS procedure was associated with a longer overall survival duration when compared to conventional distal pancreatectomy and splenectomy in univariate analysis, but this was not the case in multivariate analysis. The authors concluded their study with the notion that although the RAMPS procedure is capable of harvesting more lymph nodes than a conventional

procedure, it did not lead to better overall survival. This is, in part, due to the similar R0 rates. Looking specifically at the nature of resection, the authors state that in the RAMPS procedure there was one R2 resection and there were three R1 resections. The R2 resection was due to tumor invasion in the celiac axis, SMA, portal vein, and renal vein. Two of the three R1 resections were due to tumor invasion in the celiac axis and SMA while the other R1 resection was due to tumor invasion in the SMA and SMV. The conventional approach was associated with three R2 resections and five R1 resections. Three of the five R1 resections had a positive tangential margin and the other two had microscopic tumor involvement at the celiac axis and portal vein.

It is important to review the details of these resections because those patients identified in the R2 and R1 groups discussed above would typically be considered locally advanced or borderline resectable at best by the current guidelines in the United States. Those patients would not be offered an upfront operation for curative intent. They would typically be offered systemic chemotherapy or neoadjuvant therapy depending on the exact configuration of the tumor.

Extended Pancreatectomy with Major Arterial Resection

Distal pancreatectomy with celiac artery resection (DP-CAR) is a truly radical resection that is occasionally used for left pancreas cancer. The procedure is sometimes named after a Canadian surgeon, Lyon Appleby, who described gastrectomy with en bloc resection of the celiac and common hepatic arteries as a treatment for advanced stomach cancer in 1952. When applied to pancreatic adenocarcinoma, the celiac trunk and distal common hepatic artery (just proximal to the GDA) are transected and these structures are removed en bloc with the distal pancreas specimen. Without reconstruction, blood flow to the liver is dependent on collateral flow from the pancreaticoduodenal arcade to the GDA, which will supply the proper hepatic artery (see Fig. 19.7). In an effort to prevent liver ischemia, there are two techniques that can be employed. The first utilizes preoperative coil embolization of the common hepatic artery which allows for collateral pathways to develop before the patient is taken to the operating room for resection. The second is to perform a graft from the aorta to the

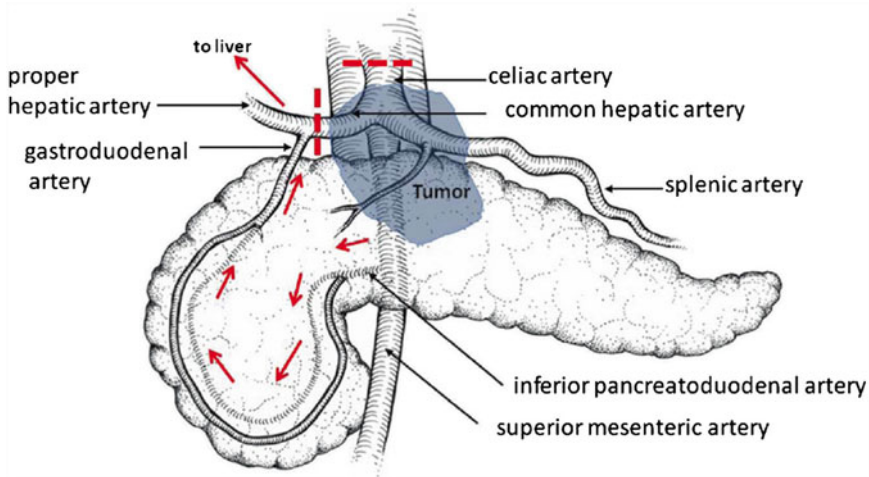

Fig. 19.7 Collateral pathway for blood supply to liver after DP-CAR. Tumor involves the celiac and common hepatic arteries. Lines of transection of these arteries are shown (*red-dashed lines*). Blood supply depends on retrograde flow (*red arrows*) from the SMA, through the inferior pancreaticoduodenal artery and its branches and continues retrograde into the GDA through its branches. From there, flow is via the proper hepatic artery to the liver. This pathway also must supply the stomach by flow into the right gastric artery from the proper hepatic artery and the right gastroepiploic artery through the GDA. (*Reproduced with permission from* [4])

common hepatic artery stump at the time of the initial operation.

Ischemia of the stomach is also a concern with DP-CAR as perfusion to this organ is similarly dependent on flow from the pancreaticoduodenal arcade into the GDA. The GDA will then theoretically perfuse the stomach through an intact right gastric and right gastroepiploic artery.

Much of the literature on DP-CAR has come from small studies conducted in Japan and is discussed more extensively elsewhere (see Chap. 15). In the United States we consider patients requiring a celiac resection locally advanced and advocate for neoadjuvant chemotherapy followed by chemoradiotherapy. The use of an initial nonoperative approach allows for the identification of those patients with aggressive cancers who progress to metastatic disease and who will not benefit from surgery. If there is no systemic progression, and the celiac artery remains involved, a DP-CAR is performed. Given the unproven benefit of this approach we perform this procedure in selected patients with better-than-average performance status.

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Palliative Operations for Unresectable Pancreatic Cancer

20

Hishaam Ismael and Brian Badgwell

Introduction

Adenocarcinoma of the pancreas is one of the most aggressive malignancies in the United States. Despite advances in imaging, chemotherapy, and surgical techniques, the 5-year survival rate remains at a dismal 5 %. With a mortality rate that is dangerously close to its incidence, pancreas cancer continues to be the fourth leading cause of cancer-related deaths in the United States [1]. Only 20–30 % of newly diagnosed cases are amenable to surgical resection and over 50 % of patients have distant disease at presentation. Surgical resection provides the best chance for long-term survival. With careful patient selection, surgery and adjuvant treatment has been shown to improve 5-year survival to over 20 % [1, 2]. Follow-up surveillance has shown that about 70 % of all patients develop metastatic recurrence even after successful surgical resection [3]. As a result, many pancreas specialists treat pancreas cancer as a systemic disease and consider palliation of symptoms and quality of life early on. Knowledge of the various palliative operative and non-operative procedures is critical in the multidisciplinary treatment of this disease. Palliative care for pancreas cancer encompasses a large number of medical, procedural, and surgical interventions that have evolved over the years. There are several surgical interventions available; some prophylactic and others designed for symptomatic relief. It is important to understand their benefits, applicability, and outcomes when compared to less invasive procedures.

Symptoms of Advanced Stage Disease

The most common symptoms requiring palliative intervention in advanced pancreatic cancer include: obstructive jaundice, gastric outlet obstruction, abdominal pain, and weight loss [4]. At the time of diagnosis, 80–90 % of all patients with pancreatic cancer present with obstructive jaundice. This results from tumor involvement of the intrapancreatic portion of the distal common bile duct. Biliary drainage has been shown to reduce the associated nausea, pruritis, and cholangitis and improve the quality of life. Malignant gastroduodenal obstruction is a late complication from the local extension of carcinoma of the pancreas, occurring in up to 20 % of patients [5]. In addition to mechanical obstruction, many patients develop delayed gastric emptying due to the

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involvement of the celiac nerve plexus. Together, mechanical and function obstruction lead to nausea, vomiting, and weight loss.

Pain control remains a formidable challenge in the palliative management of pancreas cancer. Forty to eighty percentage of patients present with pain at the time of initial diagnosis [6]. Known for its perineural extension, pancreas cancer may infiltrate the celiac or mesenteric nerve plexus causing severe back pain. The tumor may also obstruct the pancreatic duct, resulting in recurrent pancreatitis and additional pain. The association between pancreas cancer and depression has been observed and explored for over 70 years [7]. Although pain may play a role, the most common theories involve the release of serotonin by the tumor. Vomiting, pain, and depression, along with Tumor Necrosis Factor—α (TNFα), contribute to the cachexia that occurs in more than 80 % of patients with advanced disease. This anorexia–cachexia process has been shown to hasten death, reduce response to treatment, and exacerbate treatment toxicities [8].

Hence, the goals of palliative intervention should aim at relieving obstructive jaundice, gastric outlet obstruction, and decreasing pain and weight loss.

Obstructive Jaundice

There are several modalities available to decompress the biliary tree: placement of a percutaneous transhepatic biliary drain catheter (PTC), ERCP with stenting and surgical bypass. Endoscopic stent placement is preferred to PTC as the latter is associated with more pain and complications. As such, a PTC is usually reserved for situations where the less invasive endoscopic stent placement is unsuccessful or is not an option. The utilization of PTC drains is also more common with strictures involving the hilum and proximal biliary tree which are more challenging for endoscopic decompression.

ERCP with stent placement is usually the first step in the management of obstructive jaundice. This procedure has evolved since its inception in 1980 and now serves as the predominant modality for palliating obstructive jaundice with a success rate of >90 % [9]. Endoscopic stent placement is usually safe and effective; however, stents are prone to infection, occlusion, and migration. Several types of stents are available to address these complications. Plastic stents are slowly being replaced by short self-expanding metallic stents (SEMS) due to their better long-term patency (9 months vs. 4 months) [10, 11]. Metal stents can be bare or covered with PTFE to prevent tumor in-growth. Covered stents, however, are associated with higher rates of migration and cholecystitis from cystic duct occlusion.

Palliative surgical options consist of bypassing the obstruction through a loop hepaticojejunostomy, a Roux-en-Y hepaticojejunostomy, or the less commonly performed choledochoduodenostomy or cholecystojejunostomy. When compared to plastic stent placement, surgery is associated with a higher complication rate but much lower rate of reintervention [12–15]. Although more durable, the median survival for patients undergoing surgical palliation is around 6 months. As a result, surgical bypass should be considered if a patient is determined to be unresectable at the time of exploration and is expected to survive beyond 3–6 months. Randomized trials comparing endoscopic stenting and surgical bypass for palliation are summarized in Table 20.1.

A hepaticojejunostomy is the standard palliative biliary bypass technique. A side-to-side choledochoduodenostomy is generally avoided as tumor progression can result in recurrent obstruction and cholangitis. It is also associated with a higher rate of hepatolithiasis, cholangitis (10–15 %), and the rare "sump syndrome" where the distal bile duct serves as a reservoir for stones and debris [16]. A cholecystojejunostomy, although technically easier to perform, relies on cystic duct patency to divert bile flow. Endoscopic studies of the hepatocystic junction suggest that only 50 % of incoming patients will be candidates for a cholecystojejunostomy. In addition, the tumor may involve the hepatocystic junction as it progresses leading to recurrent jaundice. A study utilizing Surveillance, Epidemiology, and End Results Medicare claims data demonstrated that

patients treated with a cholecystojejunostomy had a biliary intervention rate of 7.5 % compared to 2.9 % for those treated with a hepaticojejunostomy at 1 year [17]. Recent reports indicate that a laparoscopic cholecystojejunostomy can be performed safely with a low rate of recurrent biliary obstruction [18]. This discrepancy between open and laparoscopic results warrants further investigation, however, and hepaticojejunostomy must be considered the optimal current palliative surgical approach for unresectable pancreas cancer. Laparoscopic hepaticojejunostomy is being performed with favorable outcomes. It is associated with less pain, earlier return of bowel function and a shorter hospital stay when compared to the open approach [19]. These studies, however, were small and the procedure requires advance laparoscopic skills to master. Robotic biliary bypass has been reported in the management of locally advanced pancreas cancer. To date, there is insufficient evidence to demonstrate superiority of the technique to the laparoscopic approach.

Roux-en-Y Hepaticojejunostomy

After determining that the tumor is locally advanced and a palliative hepaticojejunostomy is indicated, a cholecystectomy is performed and the hepatic duct is transected using electrocautery. A bulldog is placed on the proximal duct to reduce bile spillage. Care is taken not to injure a replaced right hepatic artery. The distal duct is oversewn with 4-0 Prolene. The jejunum is transected 20 cm from the ligament of Treitz with a GIA stapler and a 60-cm Roux limb is brought up in for an end-to-side anastomosis. The anastomosis is completed using interrupted 4-0 PDS sutures. It is important to incorporate the jejunal mucosa into the anastomosis with great care as to prevent transient biliary obstruction from edematous non-included mucosa [20]. The alimentary limb is joined to the Roux limb in a stapled or hand-sewn side-to-side or end-to-side fashion.

Other suitable options include a loop hepaticojejunostomy or a side-to-side hepaticojejunostomy without dividing the bile duct. A Roux-en-Y reconstruction, however, is associated with less anastomotic tension, postoperative cholangitis, and may lessen the clinical severity of potential biliary leaks.

Gastric Outlet Obstruction

Gastric outlet obstruction significantly affects quality of life through intractable nausea, vomiting, and abdominal pain. The resulting dehydration, electrolyte abnormalities, and malnutrition can delay the administration of palliative chemotherapy. Delayed gastric emptying can be differentiated from mechanical obstruction using endoscopy and radiographic studies, although it is important to realize that both conditions can coexist. Delayed gastric emptying should be managed medically using prokinetic agents, and procedural interventions should be reserved for mechanical gastroduodenal malignant obstruction.

The palliation of mechanical obstruction can be performed endoscopically or surgically. Endoscopic procedures include self-expanding enteral stents or endoscopically placed gastrostomy tubes/gastrojejunostomy tubes. Self-expanding metallic stent design is similar to that used for biliary stenting but duodenal stents are longer and have a larger caliber (18–23 mm). Studies examining the efficacy and safety of endoscopic stenting using enteral SEMS report a shorter time to oral intake, shorter hospital stay, and lower morbidity and mortality compared to surgical approaches [21–24]. During follow-up, however, 30–40 % of patients develop recurrent duodenal obstruction from tumor ingrowth or stent migration [25]. Duodenal stents can land or migrate to cover the ampulla of Vater and have been associated with a higher rate of major complications including duodenal perforation [20]. These results indicate that endoscopic stenting is associated with lower immediate complications but less durability and a higher reintervention rate. As such, a surgical bypass procedure should be performed in patients with anticipated longer survival. Studies comparing endoscopic stenting to gastrojejunostomies are summarized in Table 20.2.

Table 20.1 Prospective randomized trials comparing biliary stent and catheter placement to surgical bypass for biliary obstruction

Author	Year	N	Technical success (%)		Morbidity (%)		Mortality (%)		Recurrence (%)	
			Stent	Surgery	Stent	Surgery	Stent	Surgery	Stent	Surgery
Bornman et al.	1986	50	84	76	28	32	8	20	38	16
Shepard et al.	1988	52	82	92	7	14	9	20	30	0
Anderson et al.	1989	50	96	88	36	20	20	24	28	16
Smith et al.	1994	201	94	95	11	29	3	14	34	2
Artifon et al.	2006	30	100	100	40	60	0	0	20	0

N number of patients

Placement of a gastrostomy tube (G-tube) or gastrojejunostomy tube (GJ-tube) can be performed endoscopically or placed by Interventional Radiology (IR). G-tubes help improve nausea and allow for the removal of the nasogastric tube (NGT). This may allow for some liquid intake and discharge home. Median survival rates after G-tube placement are low, however, and have been reported with ranges as low as 13–17 days [26, 27]. Some studies indicate that endoscopic placement may be associated with a lower complication rate when compared to IR placement [28]. Occasionally, if the duodenum is not completely obstructed and the procedure is technically feasible, a GJ-tube can be placed for distal nutrition.

Palliative surgical options include a loop versus Roux-en-Y gastrojejunostomy performed open or laparoscopically. The concept of prophylactic gastrojejunostomy (GJ) for asymptomatic patients with unresectable pancreas cancer found at the time of attempted resection has been addressed in several studies. Based on level 1 evidence, a gastrojejunostomy should be performed in most cases, unless a life expectancy of less than 3–6 months is expected [29, 30]. Although prophylactic surgical bypass adds to operative time, it does not increase operative morbidity/mortality or length of hospital stay and is associated with a marked decrease in the rate of developing gastric outlet obstruction. A study from John Hopkins Medical Center randomized 87 patients with unresectable pancreas cancer and no risk of duodenal obstruction, identified intraoperatively, to prophylactic gastrojejunostomy versus no gastrojejunostomy. None of the 44 patients who underwent a gastrojejunostomy developed gastric outlet obstruction, while 19 % of patients who did not receive a GJ developed obstruction and required an intervention. Postoperative morbidity rates were comparable (gastrojejunostomy 32 %, no gastrojejunostomy 33 %) and mean survival for both groups was 8.3 months [29]. A similar study from the Netherlands comparing biliary bypass versus biliary and gastric bypass reported much lower rate of gastric outlet obstruction in patients who received a prophylactic gastrojejunostomy (6 % vs. 41 %) [30].

Gastrojejunostomy

Historically, most surgeons avoided a retrocolic gastrojejunostomy due to concerns of placing the anastomosis close to the tumor bed and the need to go through the transverse mesocolon. In addition, the antecolic approach has several theoretical advantages: a more mobile jejunal loop with less angulation and further away from a possible pancreatic leak. There is no convincing evidence, however, that an antecolic approach prevents late anastomotic failure. There are several studies comparing the antecolic and retrocolic approaches with particular focus on the incidence of delayed

Table 20.2 Palliative endoscopic stenting versus gastrojejunostomy for gastric outlet obstruction

Study	Number of patients		Morbidity (%)		Hospital stay (Days)		Reintervention rate (%)		Time to tolerate a diet		Notes
	ES	Surgery	ES	Surgery	ES	Surgery	ES	Surgery	ES	Surgery	
No et al. 2014 (2001–2010)	72	41	9.7	7.3 *p=0.74*	16	18 *p=0.12*	43	5.5 *p<0.01*	2	5 *p=0.046*	Late complications: tumor ingrowth, stent migration and perforation: ES=44.4 % GJ=12.2 % *p*<0.001
Khashab et al. 2013 (2001–2010)	12	227	11.7	22.1 *p=0.02*	10.1	13 *p<0.01*	27.3	8.7 *p<0.01*	NR		
Jeurnink et al. 2010 (2006–2008)	21	18	38	28 *p=0.02*	5	8 *p<0.01*	33	11 *p<0.01*	NR		
Mehta et al. 2006 (2002–2005)	13	14	17	62	5.2	11.4 *p=0.02*	NR		NR		GJ were done laparoscopically
FIori et al. 2004 (2001–2002)	9	9	22.2	22.2	3.1	10 *p<0.01*	11.1	0	2.1	6.3 *p <0.01*	Follow-up for 3 months only

ES endoscopic stenting, *OR* odds ratio

Table 20.3 Studies comparing antecolic vs. retrocolic gastrojejunostomies

Study	Year published	Study period	Number of patients (antecolic vs. retrocolic)	Antecolic (%)	Retrocolic (%)	Significance
Imamura et al.	2014	2005–2011	$n=116$ 58 vs. 58	DGE = 12.1	DGE = 20.7	$p=0.32$
Kurahara et al.	2011	2007–2010	$n=46$ 24 vs. 22	DGE = 20.8	DGE = 5	$p=0.04$
Gangavaiker et al.	2011	2006–2008	$n=72$ 32 vs. 36	DGE = 34	DGE = 28	$p=0.60$
Nikfarjam et al.	2009	2002–2008	$n=72$ 36 vs. 36	DGE = 14	DGE = 39	$p=0.02$
Hatel et al.	2005	1996–2003	$n=200$ 100 vs. 100	DGE = 5	DGE = 24	$p<0.01$

DGE delayed gastric emptying

gastric emptying. Some studies favor an antecolic approach while others did not find any correlation between the method of construction and DGE [31–35]. A recent randomized controlled trial compared patients with an antecolic ($n=121$) and retrocolic ($n=125$) reconstruction and found no significant difference in the rate of DGE (34 % vs. 36 %) [36]. A recent retrospective study from Massachusetts General Hospital looked at 800 patients and compared antecolic ($n=400$) vs. retrocolic ($n=400$) approaches. The study concluded that an antecolic approach was associated with a decreased rate of low grade "Grade A" DGE only ($p=0.038$) [37]. With such controversial data, the method of reconstruction should be based on the surgeon's experience and comfort level. Studies comparing the antecolic and retrocolic approaches are summarized in Table 20.3.

The loop of jejunum should be anastomosed to the most dependent portion of the greater curvature of the stomach to facilitate emptying [38]. The gastrojejunostomy can be hand-sewn (interrupted, continuous, single layer, double layer) or stapled. A Roux-en Y reconstruction is generally not necessary as it requires an extra anastomosis and maybe associated with Roux stasis syndrome and functional non-emptying of the stomach. It is our institutional preference to perform a loop gastrojejunostomy. When performing a double-bypass, a loop gastrojejunostomy is performed proximal to the jejunojejunostomy of a Roux-en-Y hepaticojejunostomy, as outlined in Fig. 20.1a. Alternately, the gastrojejunostomy can be fashioned utilizing the Roux limb as in Fig. 20.1b, although this may predispose the patient to bile reflux gastritis. A few studies have looked at laparoscopic gastrojejunostomies in unresectable pancreas cancer and malignant gastric outlet obstruction and reported a lower rate of complications, a shorter hospital stay, and a shorter time to tolerating solid food. A vagotomy is not performed to decrease the incidence of DGE, and patients are placed on life-long proton pump inhibitors for acid suppression. As such, we recommend a laparoscopic gastrojejunostomy as a palliative option for surgeons with advanced laparoscopic skills.

Pain

Most patients with pancreas cancer develop pain, especially those who present with locally advanced or unresectable disease. The tumor has a propensity for perineural invasion and neuropathic spread, often to the celiac plexus. Medical management consists of the administration of opioids and treatment of drug-related nausea and constipation. Several procedural interventions exist: percutaneous, endoscopic, and open celiac blocks.

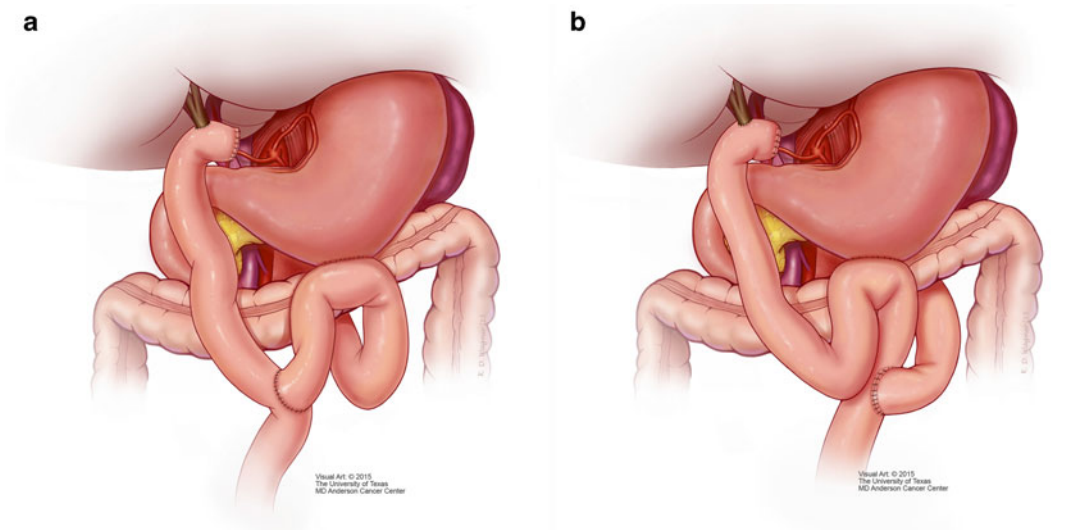

Fig. 20.1 Roux-en-Y end-to-side hepaticojejunostomy with loop gastrojejunostomy fashioned utilizing (**a**) jejunum proximal to jejunojejunostomy or (**b**) Roux limb

A Cochrane Database systemic review that included six randomized control trials demonstrated that celiac plexus block (CPB) was superior to analgesic therapy for pain relief [39]. Percutaneous CPB can be performed using ultrasound, fluoroscopy, or computed tomography. Endoscopic ultrasound-guided CPB was first described in 1996 and has gained wide acceptance due to its safety profile. The procedure is transgastric and the injection usually consists of a mixture of alcohol and bupivacaine. Several randomized controlled trials comparing percutaneous and endoscopic CPB exist and results favor the endoscopic approach [40].

Surgical Celiac Plexus Neurolysis

Surgical CPB is usually reserved for the finding of unresectable pancreas cancer at laparotomy. The procedure has proven beneficial for patients with or without preoperative pain. A prospective randomized double-blind study from John Hopkins Medical Center looked at 137 patients and randomized them to chemical splanchnicectomy versus placebo. Chemical splanchnicectomy prevented or delayed the occurrence of pain in the asymptomatic group and significantly lowered pain scores for those who had pain preoperatively ($p < 0.05$) [41].

The procedure involves the injection of 20 mL of 50 % alcohol on both sides of the aorta at the level of the celiac axis [41]. The index and middle fingers are placed around the aorta and moved down to the celiac axis. A 22-gauge spinal needle is used to infiltrate the peri-celiac retroperitoneum with the neurolytic agent. Laparoscopic CPB provides a minimally invasive approach for pain control in unresectable pancreas cancer patients identified during diagnostic laparoscopy. Studies have shown that this approach is both safe and efficacious [42]. After pneumoperitoneum is established, three 5-mm laparoscopic trocars are placed: 2 in the right subcostal area (liver retractor and working port), and another working port in the left subcostal area. The stomach is retracted laterally, and the liver is retracted anteriorly. The gastro-hepatic ligament is divided to enter the lesser sac. The stomach is lifted anteriorly and the celiac plexus/base of the left gastric artery is identified. The injection can then be delivered percutaneously or using a laparoscopic

ultrasound probe that has a small channel to direct the needle under direct vision. A 12 mm port is needed for the ultrasound probe.

Thoracoscopic neurotomy (T5–T12) is now rarely used but has been shown to reduce pain scores by 50 %.

Irreversible Electroporation

Irreversible electroporation (IRE) has recently been added as an additional ablative option in patients with locally advanced cancers involving vital structures. When IRE is delivered appropriately, it only affects the target tissue and spares the surrounding structures [43]. It can be used to target lesions that are unresectable due to extensive vascular involvement. Velanovich et al. compared 54 patients who received systemic therapy and IRE to 85 patients who received standard chemotherapy and/or chemoradiation alone. The study demonstrated an improvement in local progression-free survival (14 months vs. 6 months), distant progression-free survival (15 months vs. 9 months), and overall survival (20 months vs. 13 months) in unresectable patients who underwent IRE [44]. The use of this technology for palliation may prove beneficial, especially with advances in adjuvant therapy.

Palliative Pancreaticoduodenectomy

Pancreaticoduodenectomy is a major surgery that is generally reserved for patients who are candidates for curative resection. Morbidity and mortality rates associated with this procedure continue to improve, and as a result, the concept of palliative resection is raised from time to time. There are no randomized trials for palliative resection versus bypass surgery. Available studies have many limitations: many combine R1 and R2 resections in the same group and compare it to surgical bypass. Other studies do not meet criteria for preemptive palliation as patients underwent resection with a curative intent. Differences in survival favoring resection can therefore be explained by selection bias, as patients who undergo surgical bypass might be more advanced than those who end up with a curative resection but positive margins. Some studies have reported a survival advantage with palliative resection and recommended it for high-volume centers [45]. A systemic review of four cohort studies comparing palliative R2 resection versus bypass surgery found no clear indication for palliative resection. Palliative resections were associated with significantly increased operating times, hospital stays, and overall morbidity and mortality in comparison with palliative bypass procedures [46]. A study from Germany compared 42 patients who underwent palliative pancreaticoduodenectomy to 154 patients who underwent surgical bypass and concluded that the bypass group had a better quality of life [47]. Currently, there is insufficient data to support performing a pancreaticoduodenectomy for palliation and a survival advantage, if present, is offset by increased morbidity and decreased quality of life.

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