Chapter 6
Pancreas Adenocarcinoma and Ampullary Cancer

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Introduction

Patients who present with painless jaundice represent a challenging diagnostic dilemma. The development of painless jaundice, particularly if associated with older age, weight loss, or worsening diabetes, may be due to a periampullary tumor, such as pancreatic ductal adenocarcinoma (PDAC), ampulla of Vater adenocarcinoma (AVAC), duodenal cancer, or distal cholangiocarcinoma. This chapter focuses on both PDAC and AVAC, as they are the most common malignancies arising in the periampullary region. PDAC is the most common periampullary tumor and is the tenth most common cancer in the USA [1]. In 2015, it was estimated that 46,420 people would be diagnosed with PDAC, and of those diagnosed, 39,590 were expected to die of this disease [2]. Importantly, it has been recognized that the majority of patients with PDAC may have distant metastases at the time of diagnosis, even in the absence of radiographic evidence of disease [3]. As such, the oncologic management of PDAC has evolved to emphasize

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the early administration of systemic therapy for virtually every stage of disease. In addition, multiple randomized clinical trials have demonstrated that even in earlier stage disease, patient survival is improved with multimodality therapy and that surgery by itself is rarely curative. In comparison to PDAC, AVACs are more common in men, present with small tumors, and in general are less biologically aggressive [4]. As a result, multimodality therapy is often administered selectively in AVAC based on the pathologic stage. Given the combined prevalence of these two malignancies, most health care providers will encounter patients with one of these diseases at some time throughout their practice in medicine. The goal of this chapter is to describe the clinical staging system and treatment options for patients with PDAC and highlight how the management of AVAC may differ from PDAC. This chapter also provides a background for primary care providers which may help to address concerns raised by patients and families impacted by these diseases.

Question 1: I Was Told that I Have Pancreatic Cancer. How Advanced is My Cancer?

Answer: Oncologists rely on staging systems to help communicate information regarding prognosis and to assist with appropriate treatment planning. Staging is particularly critical for PDAC, since operative interventions can be particularly complicated and require a significant postoperative recovery. As such, surgery should be reserved only for patients who will derive a significant benefit from the removal of the primary tumor. The clinical stage is determined by physical exam and radiographic imaging. The four clinical stages of PDAC from least to most advanced are: resectable, borderline resectable, locally advanced, and metastatic disease (Table 6.1). The former two stages are considered to represent operable disease, and therefore, may be amenable to multimodality therapy and surgical resection.

Table 6.1 Comparison of National Comprehensive Cancer Network clinical staging definitions and the Medical College of Wisconsin staging definition

Stage	MCW	NCCN
Resectable		
SMA, Celiac	No abutment	No abutment
Hepatic artery (HA)	No abutment	No abutment
SMV/PV	≤50 % narrowing of SMV, PV, SMV/PV	No abutment, distortion, tumor thrombus or encasement
Borderline resectable		
SMA, Celiac	≤180°	<180°
Hepatic artery (HA)	Short segment encasement*	1 GDA encasement up to the HA or 2 direct abutment of HA w/o extension to celiac axis
SMV/PV	>50 % narrowing of SMV, PV, SMV/PV*	1 Impingement and narrowing of the lumen 2 Encasement or short segment venous occlusion*
Other	CT scan findings suspicious but not diagnostic of metastatic disease	
Locally advanced		***Unresectable***
SMA, Celiac	>180°	>180°
SMV/PV	Occlusion w/o option for reconstruction	Unreconstructable SMV/PV
Metastatic		1 Aortic invasion or encasement
Extrapancreatic disease	Peritoneal or distant metastases	2 LN metastases beyond the field of resection

*Amenable to vascular reconstruction

The latter two stages are considered to be inoperable disease, and are best treated with chemotherapy with or without radiation therapy. If a patient undergoes surgery, pathologic stage can be further refined based on characteristics of the resected specimen. However, unlike other less aggressive solid tumors, in which pathologic staging is used to direct additional therapy after surgery (adjuvant therapy), pathologic staging for PDAC (Table 6.2) does not change the recommendation in favor of adjuvant therapy and therefore is of more limited utility.

Clinical stage is determined by the relationship between the tumor and adjacent vascular structures. The gold-standard diagnostic study used to define this relationship is a computed tomography (CT) scan with both late arterial and portal venous phases (dual phase). Dual phase CT imaging defines the relationship of the tumor to major venous (superior mesenteric vein [SMV]/portal vein [PV]) and arterial (superior mesenteric artery [SMA], celiac artery [CA]) structures and may identify the presence of metastatic disease. As a rule, patients with a new diagnosis of PDAC should be presented in a multidisciplinary conference to gain the input of dedicated abdominal radiologists, surgeons, medical oncologists, and radiation oncologists, in order to accurately determine clinical stage, consider available clinical trials, and develop the best overall treatment plan.

Initial Evaluation of a Patient with PDAC

The diagnostic evaluation of a patient with suspected PDAC begins with a detailed history and physical examination. Symptoms associated with PDAC may vary depending on tumor location, with tumors located in the head of the pancreas causing painless jaundice, as compared to tumors located in the body and tail of the pancreas, which may cause back pain. Other common signs and symptoms include weight loss (51 %), abdominal pain (39 %), nausea/vomiting (13 %), and pruritus (11 %) [6]. Risk factors for PDAC include advanced age, smoking, chronic pancreatitis, diabetes

TABLE 6.2 AJCC PDAC Staging [5]

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas, but without involvement of the celiac axis or superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0

(continued)

Table 6.2 (continued)

Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

mellitus, and obesity. In particular, a patient who presents with weight loss and worsening diabetes is at high risk for having an undiagnosed PDAC; such patients should undergo abdominal imaging and have a referral to a pancreatic cancer specialist. In addition, a careful family history should be obtained, as approximately 10 % of patients may have a genetic predisposition for PDAC. Patients who are considered to be at high risk for PDAC (lifetime risk ≥ 10 %) are those with two first-degree family members with PDAC or three any-degree family members with PDAC [7].

A comprehensive physical examination should be performed on all patients being evaluated for PDAC. However, with the exception of jaundice, the physical exam is often unremarkable. Patients with advanced disease may have a palpable abdominal mass at the umbilicus (Sister Mary Joseph node) or supraclavicular lymphadenopathy (Virchow's node) on exam, suggestive of metastatic disease. One third of patients with periampullary tumors will have a palpable gallbladder (Courvoisier's sign) due to biliary obstruction resulting in gallbladder ectasia. Other relevant findings may include ascites, signs of cachexia, and venous thrombophlebitis.

The initial laboratory evaluation should include a baseline complete blood count, basic metabolic panel, and hepatic function tests. Tumor markers such as carbohydrate antigen 19-9 (CA19-9) should also be obtained. CA19-9 is a sialylated

Lewis antigen, which is an epitope found on mucins secreted by PDAC cells. Several studies have demonstrated that CA 19-9 is associated with tumor stage, resectability, and risk of recurrence [8, 9]. Very high CA 19-9 (>2000 U/mL) levels have been associated with an increased risk of having metastatic disease [10]. One of its limitations as a biomarker is that CA19-9 is not produced in approximately 10–15 % of the general population [11]. Additionally, in the setting of biliary obstruction, CA19-9 levels are commonly falsely elevated, limiting its prognostic relevance when the total serum bilirubin is greater than 2 mg/dL [12].

Imaging is essential for the clinical staging of PDAC and in the absence of palpable metastatic disease, clinical staging is impossible without high quality abdominal imaging. For this reason, it is imperative that the correct imaging modality is utilized and reviewed by an experienced radiologist, with particular emphasis on the relationship of the tumor to adjacent vascular structures. Currently, the preferred imaging modality is the multi-detector CT with IV contrast obtained in both the late arterial and portal venous phases with thin (3 mm or less) slices and with three dimensional (3D) reconstructions. The separate arterial and venous phase images are essential to defining the relationship of the pancreatic tumor to the surrounding arterial (CA and SMA) and venous (SMV and PV) structures [13].

Defining the Clinical Stage

The utilization of abdominal imaging is essential, as the pancreas is a retroperitoneal organ which is located near several critical vascular structures. Importantly, the relationship of the tumor to these vascular structures greatly impacts oncologic prognosis and the ability to be able to achieve a negative resection margin [14, 15]. Therefore, the clinical stage of disease is defined by the relationship between the primary tumor and the arterial structures (common hepatic artery, celiac artery, and SMA) and the venous structures (SMV/PV) (Table 6.1). In general, staging separates patients into two

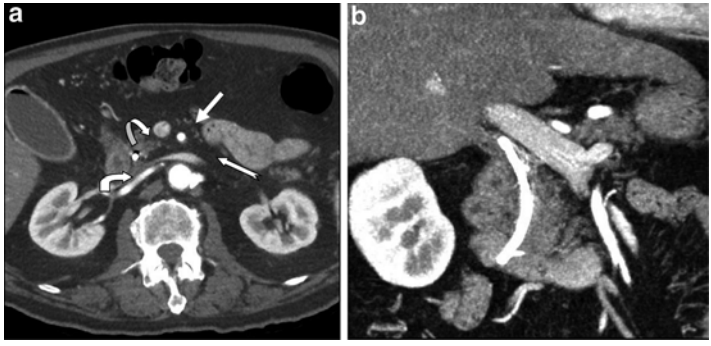

Fig. 6.1 Resectable Pancreatic Cancer, (**a**) well defined fat plane between tumor and SMA, (**b**) SMV/PV narrowing less than 50 %

categories, those with potentially localized disease (resectable or borderline resectable PDAC) or those with advanced disease (locally advanced or metastatic PDAC).

Resectable PDAC (Fig. 6.1) is defined by an absence of tumor extension to major vascular structures, including the SMA, CA, hepatic artery, or SMV/PV. Contact of a vessel with the tumor, which is characterized by the absence of normal soft tissue planes between the tumor and vessel, is defined as abutment if the contact involves $\leq 180°$ of the vessel circumference, and encasement if the contact involves $>180°$. At some institutions, the definition of resectable PDAC has been expanded to include those patients who may have SMV/PV abutment or encasement that results in less than 50 % narrowing of the vessel lumen. Historically, encasement of the SMV/PV was considered a contraindication for surgery and surgical resection was limited to patients without encasement of the SMV/PV and no abutment of the SMA. However, with evolving surgical experience, high volume pancreatic programs have reported that patients with PDAC who receive preoperative (neoadjuvant) therapy and undergo pancreatectomy with vascular resection and reconstruction experience equivalent surgical morbidity and mortality, as well as long term survival, as compared to patients who underwent standard pancreatectomy [16]. As such, at select centers, tumors which involve the SMV/

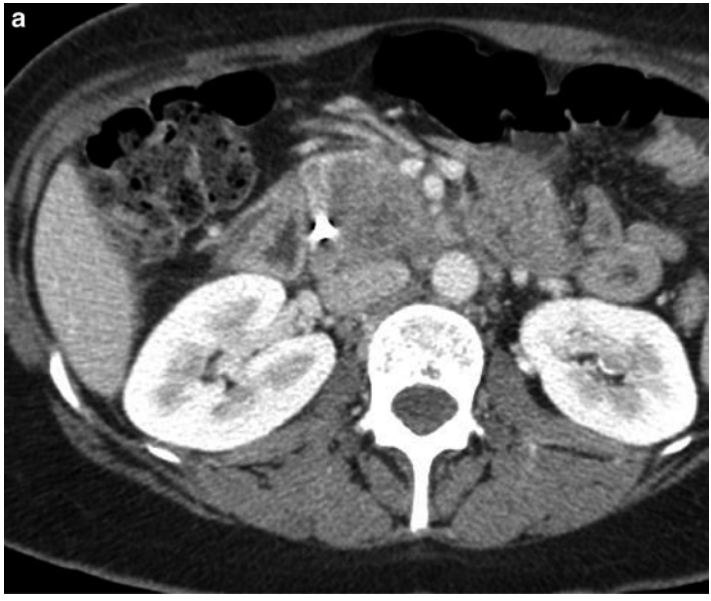

Fig. 6.2 Borderline Resectable Pancreatic Cancer. (**a**) abutment of < 180° SMA

PV without significant narrowing are considered resectable. The primary anatomic criterion which distinguished borderline resectable PDAC from resectable PDAC is the presence of tumor abutment of ≤ 180° of the SMA or CA. The borderline resectable category also includes tumor abutment/encasement of a short segment of the hepatic artery—usually at the origin of the GDA, or an occluded SMV/PV—amenable to reconstruction.

The degree of tumor–artery relationship also defines borderline resectable (Fig. 6.2) and locally advanced PDAC (Fig. 6.3). The degree of arterial abutment/encasement is critical because of the clinical observation that induction therapy may sterilize at least the periphery of the tumor thereby facilitating a complete resection, especially in patients whose tumor–artery relationship is limited to abutment. In contrast, with arterial encasement the likelihood of a margin

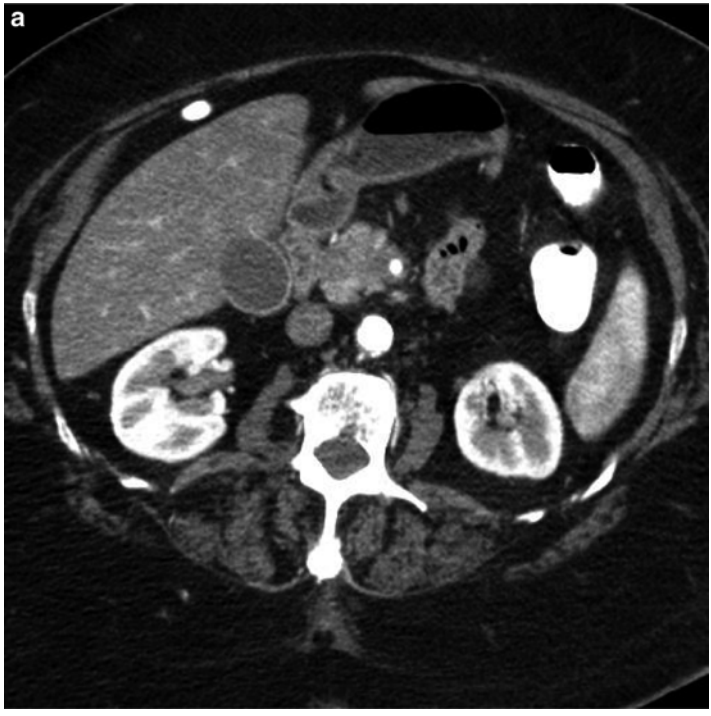

Fig. 6.3 Locally Advanced Pancreatic Cancer. (**a**) >180° involvement of the SMA

negative resection is very low, and attempted arterial resection and reconstruction in patients with large, locally advanced tumors have been associated with increased perioperative morbidity and mortality [17]. Therefore, locally advanced tumors are usually considered inoperable. In addition, the locally advanced category also includes patients with SMV/PV occlusion with no technical option for reconstruction. Since the tumor–vessel relationships are critical to staging and treatment planning, all PDAC patients, especially those without obvious metastatic disease, should have their cases presented in a multidisciplinary tumor board with dedicated abdominal imaging radiologists, surgical oncologists, medical

oncologists, and radiation oncologists all present. Finally, metastatic disease is defined by the presence of extrapancreatic metastases on radiographic imaging [18]. Importantly, a select proportion of patients may have radiographic lesions which are indeterminate for metastases (usually too small to accurately characterize or biopsy), even in the absence of SMA abutment or venous narrowing. These patients are considered by some institutions to have BLR PC, and are offered neoadjuvant therapy with the reasoning that true unequivocal metastatic disease (if present) may be detected at subsequent restaging evaluations [19].

Question 2: What Is the Difference Between Neoadjuvant Therapy and Adjuvant Therapy for PDAC?

Answer: Oncologic therapy delivered before an anticipated operation to remove the primary tumor is called "neoadjuvant" therapy, as compared to therapy which is delivered after the primary tumor is surgically excised, which is referred to as "adjuvant" therapy. Historically, patients with resectable PDAC have been treated with surgery followed by adjuvant therapy. Patients with borderline resectable PDAC are recommended to receive neoadjuvant therapy prior to surgery. However, as the understanding of PDAC tumor biology improves, neoadjuvant therapy is increasingly being adopted in the management of patients with resectable PDAC as well. It is important to emphasize that surgery alone will not be curative in the vast majority of operated patients.

Treatment of PDAC

As with other solid tumors, the treatment for PDAC is determined by the clinical stage. Simply stated, patients with metastatic disease should receive systemic therapy, while patients with localized disease may benefit from surgery if the tumor

can be completely removed. One unique aspect of PDAC biology is that the majority of patients who are diagnosed with PDAC will have metastatic disease (subclinical) regardless of radiographic findings [3]. Even among patients who appear to have resectable disease, the median survival rate with surgery followed by adjuvant therapy is only 24 months, suggesting a high prevalence of occult metastases [20, 21]. Multiple randomized controlled trials have demonstrated a survival benefit of adjuvant therapy after surgical resection for all patients regardless of pathologic stage, suggesting that there is no stage of disease that will not benefit from systemic therapy [22, 23]. While the need for systemic therapy in the management of PDAC is universally accepted, current controversies have centered on the sequencing of systemic therapy in the context of multimodality therapy. Recognizing the high risk for the development of metastatic disease, the management of every stage of PDAC has evolved to emphasize the early administration of systemic therapy prior to any locoregional therapy and is currently supported by consensus guidelines for the management of patients with borderline resectable and locally advanced PDAC [24, 25]. Arguably this rationale may be extended to patients with resectable PDAC as well.

Limitations of Adjuvant Therapy

The treatment sequencing for patients with resectable PDAC remains controversial, in particular, whether patients should receive surgery followed by adjuvant therapy (surgery-first approach) or neoadjuvant therapy followed by surgery (neoadjuvant approach). The impact of the magnitude and the complexity of a pancreatic operation on a patient's physiology should not be underestimated. Perioperative mortality associated with surgical resections of the pancreatic head (pancreaticoduodenectomy or Whipple procedure) were once reported to be as high as 30 % but with improvements in surgical technique and perioperative management, they

are currently reported to be associated with a 90-day mortality of approximately 4 %, when performed at high volume centers [26]. Significant postoperative complications occur in approximately 30 % of patients, including pancreatic fistulas, delayed gastric emptying, and infections [21]. The prolonged recovery from surgical resection is not uncommon and can be an impediment to the successful administration of planned adjuvant therapy. Analysis of the Surveillance, Epidemiologic, and End Results (SEER) database suggests that 50 % of patients who are treated with a surgery-first approach fail to receive adjuvant therapy [27]. Given the high risk of developing metastatic disease even among patients with localized PDAC, a reliance on adjuvant therapy to treat micrometastatic disease is unrealistic as it can only be successfully administered to half of the patients.

Rationale for Neoadjuvant Therapy

To address the limitations of adjuvant therapy, a growing interest has emerged in alternative treatment sequencing. Neoadjuvant therapy for PDAC has several theoretical advantages over adjuvant therapy (summarized in Table 6.2). In contrast to an adjuvant approach, neoadjuvant therapy ensures the delivery of all components of multimodality treatment to all patients who undergo a potentially curative pancreatectomy. Importantly, since neoadjuvant therapy offers an "induction" phase lasting approximately 2–3 months, individuals with unfavorable tumor biology who develop early metastatic disease are identified prior to surgery. Importantly, in the subset of patients (up to 20–30 %) who are found to have disease progression after neoadjuvant therapy (before surgery), the morbidity of an operation is avoided. For those patients who are found to have disease progression after neoadjuvant therapy, at the time of preoperative restaging, a major operation is avoided; an operation which, in retrospect, would have resulted in early disease recurrence if a surgery first treatment approach had been used. Such patients

benefit greatly from their accurate identification as a subset having accelerated tumor growth not responsive to a local therapy such as surgery. When chemoradiation is utilized as part of neoadjuvant therapy, the delivery of chemoradiation in a well-oxygenated environment improves the efficacy of radiation and decreases the toxicity to adjacent normal tissue [28, 29]. The addition of radiation has important pathologic implications with several series reporting decreased rates of positive margins and node positive disease [30–32].

Experience with neoadjuvant chemoradiation for patients with resectable PDAC suggests a survival benefit for those who complete neoadjuvant therapy and undergo successful resection of the primary tumor as compared to patients treated with a surgery first strategy who receive postoperative adjuvant therapy [33, 34]. Two clinical trials involving patients with resectable PDAC who received neoadjuvant chemoradiation and pancreaticoduodenectomy reported median survivals approaching 3 years as compared to approximately 2 years for those who complete adjuvant therapy after a surgery first approach, and less than 2 years for those who fail to receive adjuvant therapy after pancreaticoduodenectomy [20, 21, 33, 34]. In part, the survival advantage observed in the patients who were treated with a neoadjuvant approach is due to the identification of those patients with disease progression (aggressive tumor biology) after induction therapy and before surgery which removes them from consideration of pancreaticoduodenectomy. In addition, theoretical advantages of neoadjuvant treatment sequencing include the treatment of micrometastases when they are radiographically occult and perhaps more sensitive to systemic therapy, and at a time when host defenses and innate immune surveillance have not been impaired by the stress of a major operation (as systemic therapy/chemoradiation is delivered prior to surgery).

At the author's institution, outside of a clinical trial, patients with resectable PDAC are recommended to receive neoadjuvant chemoradiation based on the report of Evans and colleagues [33]. Radiosensitizing chemotherapy is given

concurrently with external beam radiation over a course of 28 fractions (lasting approximately 5.5 weeks). Restaging imaging and labs are obtained approximately 4 weeks after the last radiation dose, and in the absence of disease progression, patients are offered surgical resection. Since patients with borderline resectable PDAC are at higher risk for harboring radiographically occult distant metastases, a longer period of induction therapy is recommended for these patients. At the author's institution, patients with borderline resectable PDAC receive 2 months of chemotherapy followed by chemoradiation. Restaging imaging and labs are obtained after 2 months of induction chemotherapy and again following the completion of chemoradiation.

Importantly, multidisciplinary care is crucial in the coordinated management of PDAC. The scope of the multidisciplinary team is vast and includes medical, surgical, and radiation oncologists, diagnostic radiologists, advanced endoscopists, genetic counselors, dietitians, and endocrine specialists, all of whom play an important role in minimizing the toxicities associated with the treatment and with care coordination. All patients with PDAC undergoing neoadjuvant therapy should be reviewed at each restaging in a multidisciplinary conference to assure timely coordination of care, accurate staging, and optimal treatment planning.

Question 3: What Is Ampullary Cancer and How Is It Different from PDAC?

Answer: Ampullary cancers, or ampulla of Vater adenocarcinomas (AVAC) are neoplasms arising from within the epithelium of the ampulla of Vater. It is the second most common cancer in the periampullary region, after PDAC. Though the surgical management of ampullary and PDAC is the same (pancreaticoduodenectomy), patients with ampullary cancer who undergo a curative surgical resection have a much better prognosis.

Ampulla of Vater Adenocarcinoma

AVACs are relatively uncommon, accounting for less than 1 % of gastrointestinal cancers. Although most AVAC are sporadic, patients with familial adenomatous polyposis (FAP) have an incidence of AVAC which has been reported to range from 3 to 12 %, and the genotype of the adenomatous polyposis gene mutation can predict the clinical risk of AVAC [35]. AVACs have a higher incidence among men and due to the anatomic location, patients will often develop symptoms with small tumors, allowing for earlier detection than in the case of PDAC [4]. In addition, patients with AVAC may have a more favorable disease prognosis than patients with PDAC due both to earlier diagnosis and more favorable tumor biology. For patients with ampullary cancer who undergo a curative surgical resection, single institutional data would suggest a 5-year survival rate as high as 68 %, compared to a 20 % 5-year survival rate in patients with PDAC who undergo multimodality therapy to include a curative surgical resection [20, 36].

Initial Evaluation of a Patient with PDAC

The clinical presentation of AVAC is quite similar to that seen in PDAC [37]. Symptoms that are highly predictive of malignancy include dark urine, pruritus, and jaundice [37]. Other symptoms include nausea and vomiting, abdominal pain, pruritus, and occult gastrointestinal bleeding. The diagnostic work up should include the following laboratory studies: CBC, BMP, hepatic function panel, CA19-9, and carcinoembryonic antigen (CEA). As with PDAC, a dual phase CT scan is essential in the diagnosis and staging of AVAC. Unlike PDAC, AVAC are generally small, may not involve the adjacent pancreatic head, and can frequently be missed by CT imaging alone [38]. Additionally, endoscopic retrograde cholangiopancreatography (ERCP) is very helpful in the diagnosis of AVAC. ERCP allows for direct visualization

of the tumor site, which helps to distinguish AVAC from PDAC, and enables tissue biopsy of the papilla and ampullary segments of the pancreatic duct and common bile duct [39]. In addition, endoscopic ultrasound (EUS) has significantly improved diagnostic accuracy as compared to a dual phase CT scan, with reported 100 % positive predictive value and 61 % negative predictive value [40].

The staging system for ampullary cancer is based on the criteria developed by American Joint Cancer Committee (AJCC), and is summarized in Table 6.3. As compared to PDAC, in which the tumor stage is defined by tumor size and tumor extension to vascular structures, the tumor stage for AVAC is defined by the extent of tumor growth into the duodenum, pancreas, or peripancreatic soft tissues (Table 6.3). As expected, pathologic stage is correlated with survival; negative prognostic factors include greater tumor stage (T3-T4) and node positive disease (N1) [41]. In a recent analysis of the SEER database, which included 421 patients with T1 AVAC, only 163 patients had nodes removed for staging, and of these patients, 33 (22 %) had lymph node metastases, suggesting that even small AVACs have a high risk of nodal metastases [42].

Treatment of AVAC

Due to the rarity of the tumor, the management of AVACs has been most frequently reported as retrospective single-institution case reports. Consensus guidelines do not exist to guide the management of AVAC, which has largely been extrapolated from the management of duodenal and pancreaticobiliary cancers. While endoscopic techniques have been described for the management of small benign ampullary adenomas, for AVAC, surgical resection remains the locoregional therapy of choice for patients with localized disease. Surgical resection with a pancreaticoduodenectomy ensures negative margins and adequate lymph node sampling for optimal adequate staging [37, 42].

Table 6.3 AJCC AVAC Staging [5]

Primary tumor (T)			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor confined in the ampulla of Vater or sphincter of Oddi		
T2	Tumor involves the duodenal wall		
T3	Tumor invades pancreas		
T4	Tumor invades peripancreatic soft tissue or other organs		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Recurrence rates following surgical resection have been reported to range from 15 to 38 % for locoregional recurrences and 15–40 % for metastatic progression [36, 43, 44]. No prospective study has been performed which has evaluated the benefit of adjuvant therapy for AVAC, although some studies have included AVAC in evaluating the role of adjuvant therapy in periampullary tumors. The largest study, European Study Group for Pancreatic Cancer (ESPAC 3), contained the largest proportion of patients with AVAC of any prospective randomized study (with ~70 % of patients enrolled having AVAC); 192 patients with AVAC received adjuvant chemotherapy and 105 patients were observed [45]. Of all patients on the trial, approximately 50 % had T3 or T4 tumors and 60 % had lymph node metastases. The overall median survival of all patients who received no adjuvant therapy was 35.2 months, as compared to 43.1 months for patients in the chemotherapy arms, but this did not reach statistical significance ($p = 0.25$). However, after adjusting for other prognostic factors, the authors concluded that there was a modest benefit of adjuvant therapy for periampullary cancers. Importantly, the median survival for patients with AVAC in this trial was 53.1 months. Other large single-institution studies have demonstrated 5-year survival rates for patients with AVAC of approximately 40 % following pancreaticoduodenectomy [46, 47]. The role of adjuvant chemotherapy and radiation therapy in the management of patients with AVAC remains controversial and to date there are no published guidelines regarding the use of adjuvant therapy. However, based on collective single-institution experiences, adjuvant therapy should be considered in patients with node positive disease or T3/T4 tumors [48, 49].

One important observation from the ESPAC-3 trial was the demonstration of the challenges in administering adjuvant therapy after major pancreatic resection. Of the 289 patients randomized to receive adjuvant chemotherapy, 44 (15 %) never received any adjuvant therapy and only 140 (48 %) received all of the six planned cycles of chemotherapy. As with PDAC, the benefits of neoadjuvant treatment

sequencing may be beneficial for patients with AVAC, particularly if at diagnosis, the patients have large (T3/T4) tumors (for example, evidence of pancreatic invasion on CT or EUS) or evidence of lymph node metastases.

Conclusions

Management of patients with PDAC and AVAC starts with careful staging evaluation and the coordinated treatment planning of a multidisciplinary team. Given the magnitude of surgical interventions, adjuvant therapy may not be feasible in many patients. Therefore, consideration of neoadjuvant therapy has practical appeal and oncologic advantages, and allows patients to most effectively receive stage appropriate therapies while minimizing the toxicities of unnecessary surgery.

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