19 The Modified Appleby Procedure for Locally Advanced Pancreatic Body/Tail Cancer: How I Do It

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19.1 Introduction

Tumors of the body and tail account for approximately one-third of pancreatic cancers, and up to three-quarters of body and tail tumors are deemed unresectable on presentation [1]. Unresectability is a result of liver metastases, carcinomatosis, or local invasion of major vascular structures. Although pancreatectomy in the presence of metastatic disease has not proven beneficial, resection of locally advanced pancreatic cancer to negative margins may improve survival [2]. Treatment of locally advanced pancreatic adenocarcinoma with arterial involvement remains controversial; however, 30% of patients with locally advanced, Stage III pancreatic cancer will die without evidence of metastatic spread [3]. As such, this group of patients is most likely to benefit from an aggressive surgical approach. Neoadjuvant therapy has allowed for more careful selection of patients that may benefit from pancreatectomy with arterial resection.

Whereas locally advanced pancreatic head adenocarcinoma may invade the superior mesenteric artery, locally advanced cancers of the body and tail of the pancreas will often first invade the celiac axis or common hepatic artery. Under carefully selected circumstances, patients may undergo the modified Appleby procedure for celiac axis or common hepatic artery involvement. The Appleby procedure was originally proposed in 1953 as a treatment for locally advanced gastric cancer with bulky celiac lymphadenopathy, and consisted of en bloc resection of the celiac axis, total gastrectomy, and distal pancreatectomy with splenectomy [4]. Nimura et al. [5] in Japan first modified the procedure for advanced pancreatic cancer of the body/tail in 1976. The modified procedure consisted of distal pancreatectomy with celiac axis resection (DP-CAR). Pancreatectomy with en bloc arterial resection was introduced in the Western world by Fortner [6] around the same time; however, poor long-term survival and high morbidity led this technique to fall out of favor. It wasn't until the early 2000s that the modified Appleby procedure was endorsed in the Western world. Our group, Gagandeep et al. [7], previously demonstrated that resection of the celiac axis with or without reconstruction could be done safely with acceptable postoperative mortality. The procedure has gained more favor in recent years as morbidity with pancreatic surgery has improved, selection criteria have improved, and several major centers have shown promising results [8–10]. Furthermore, patients with locally advanced pancreatic body/tail cancer involving the celiac plexus may suffer severe

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pain, leading to a poor quality of life. The modified Appleby procedure may palliate symptoms of pain in addition to potentially providing a survival benefit.

19.2 Diagnosis

Preoperative imaging is paramount for determining resectability of pancreatic cancer and for properly planning the appropriate operation for a pancreatic mass. Computed tomography (CT) or magnetic resonance imaging (MRI) with multiphase pancreatic protocol is preferred for evaluation of local invasion associated with a pancreatic mass (Fig. 19.1). The role of positron emission tomography (PET)/CT currently is not clear in the staging of pancreatic adenocarcinoma, and PET/CT is not a mandatory examination for staging; however it may be used after performance of pancreas protocol CT imaging in high-risk patients to evaluate for metastatic disease [11]. For patients in whom neoadjuvant therapy is being considered, biopsy for proof of malignancy is required; however biopsy proof of malignancy is not mandatory if initial surgical resection is being entertained.

Special attention should be paid to the celiac axis and the superior mesenteric artery (SMA) on imaging. The liver not only receives arterial blood flow from the common hepatic artery from the celiac axis but also receives collateral blood flow through the head of the pancreas from the inferior pancreaticoduodenal arteries coming from the SMA flowing through the gastroduodenal artery (GDA). The SMA should be widely uninvolved, and the celiac axis must have a sufficient segment of normal artery to allow for safe transection at the takeoff from the aorta (Fig. 19.2). In addition, the common hepatic artery must have enough space to before the takeoff of the GDA. Replaced hepatic vessels should be noted prior to surgery to plan accordingly.

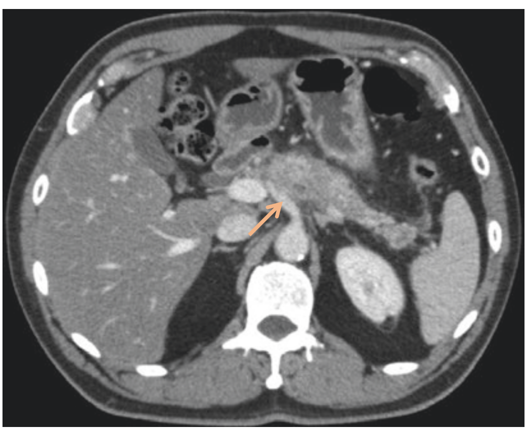

Fig. 19.1 Locally advanced pancreatic body adenocarcinoma on preoperative CT scan. The celiac axis is invaded by tumor (*arrow*)

The patient's presenting symptoms may also suggest involvement of adjacent structures by disease, and this can be confirmed on imaging. Gastric outlet obstruction or back pain may suggest a locally aggressive tumor with invasion of the stomach or the celiac plexus/retroperitoneum, respectively.

19.3 Patient Selection

The indication for the modified Appleby procedure is involvement of the celiac axis by a pancreatic body tumor without involvement of the head of the pancreas or SMA. In general, only a minority of patients are candidates for this aggressive operation. In our series, the modified Appleby procedure was performed in only 2% of patients undergoing pancreatectomy during the study period; however, the frequency of the operation has increased with time at other institutions [7, 12]. With proper selection, surgery may be successfully performed in up to 87% of patients preoperatively deemed resectable with a modified Appleby procedure [8]. Patients are selected based on their likelihood of obtaining negative margins, response to neoadjuvant therapy, lack of distant metastases, and functional capacity.

The treatment of pancreatic adenocarcinoma may require multiple modalities, and a component of patient selection may also involve the use of neoadjuvant therapy. By using a neoadjuvant treatment approach, patient selection may be further refined to those patients who will most

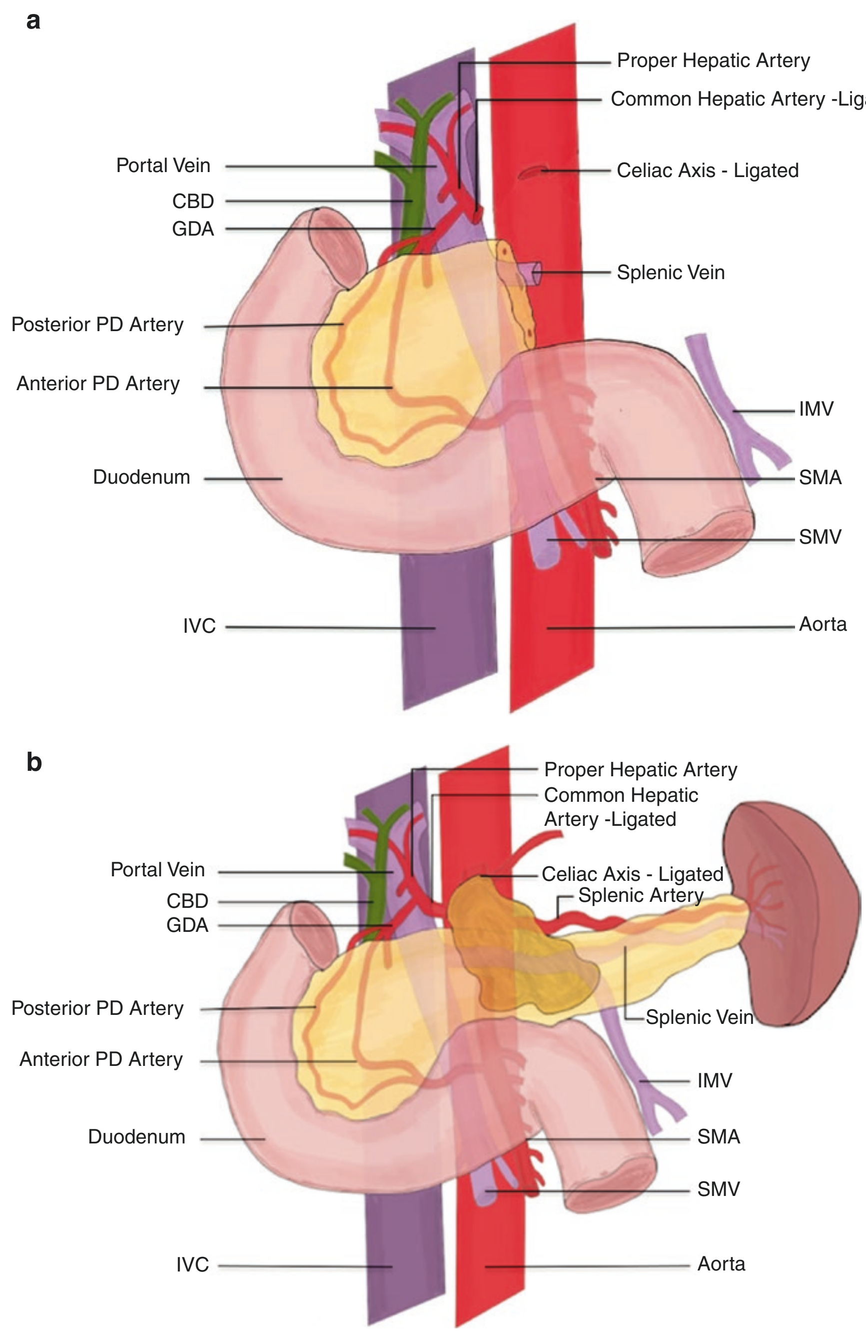

Fig. 19.2 (**a**) Illustration of a locally advanced tumor of the body of the pancreas. Tumor involves the celiac axis. (**b**) Anatomy after modified Appleby procedure. Ligation of the common hepatic artery and celiac axis are required. Blood flood to the liver is based on collaterals from the superior mesenteric artery to the gastroduodenal artery. *CBD* common bile duct, *GDA* gastroduodenal artery, *PD* pancreaticoduodenal, *IVC* inferior vena cava, *IMV* inferior mesenteric vein, *SMA* superior mesenteric artery, *SMV* superior mesenteric vein

benefit from a major resection. Approximately 20% of patients with locally advanced pancreatic adenocarcinoma are considered surgical candidates using this strategy, thus eliminating those patients who would not benefit from a major operation [8].

19.4 Surgical Technique

A safe and efficient operation is ensured by adequately selecting the ideal patient for a modified Appleby procedure. Locally advanced pancreatic cancers are at risk of undiagnosed metastases; therefore, a diagnostic laparoscopy is advisable at the time of the planned resection. A laparotomy incision is made once the liver and the peritoneal surfaces have been examined without evidence of metastatic disease. We prefer a bilateral subcostal incision because this allows access to the pancreas in its entirety, the spleen, and the porta hepatis; however, a midline incision may also be used.

19.4.1 Determining Resectability

Diagnostic laparoscopy is usually not enough to provide enough information to determine resectability. The pancreas must be fully examined by opening the lesser sac and performing an extended Kocher maneuver. The pancreas is examined to appreciate the mass in relation to vital structures, with particular attention paid to the celiac axis, SMA, and GDA. The fundamental principle underlying the operation requires flow to the liver from collaterals through the pancreatic head from the SMA to the GDA (Fig. 19.2). In our early experience, we would perform an angiogram to confirm good collateral circulation; however, we subsequently feel that angiography is not necessary after observing very little variation in the well-preserved blood supply through the head of the pancreas. Once adequate exposure is obtained, resectability is ultimately determined by clamping the common hepatic artery and verifying blood flow to the proper hepatic artery and liver via the GDA. In the case of poor blood flow, the common hepatic artery may be reconstructed to restore blood flow if the tumor can still be safely removed off of the aorta.

19.4.2 Dissection of the Celiac Trunk

The celiac trunk is accessed both anteriorly and posteriorly. By performing a cholecystectomy and portal node dissection, the proper hepatic artery, GDA, and common hepatic artery can be identified and traced to the level of tumor involvement. Once the common hepatic artery is isolated with a vessel loop, the common hepatic artery is clamped to verify flow from the GDA into the proper hepatic artery. It is at this point that the extent of celiac axis involvement is often appreciated.

Attention is then turned to separation of the transverse mesocolon from the omentum by entering the lesser sac. The gastrocolic ligament is divided followed by the lienocolic ligament allowing for caudal retraction of the colon. The peritoneum along the inferior border of the pancreas is incised, and the pancreas and spleen are lifted up from the retroperitoneum in the avascular plane. We divide the distal splenic artery early to allow the spleen to decompress. The dissection of the pancreatic body/tail starts at the inferior border of the spleen, followed by division of the lienorenal and lienophrenic ligaments, and then this dissection is carried over until the pancreas is completely freed from the retroperitoneum up to the superior mesenteric vein (SMV) and PV.

Posteriorly, the celiac artery is approached in one of two ways. If the PV can be completely freed from the neck of the pancreas, the pancreas may be divided allowing access to the base of the celiac trunk. The surgeon should be committed to the operation prior to dividing the pancreas. Taking down the attachments of the spleen and distal pancreas may also expose the aorta and takeoff of the celiac trunk. The spleen and distal pancreas are rotated medially while separating the avascular plane posterior to the pancreas. From here, both the celiac artery and SMA are identified. The SMA is examined for any tumor involvement and then freed from any attachments to the body of the pancreas. The celiac artery is examined for extent of tumor involvement and is completely encircled. A vascular clamp is placed across the base of the celiac artery, and blood flow to the liver and stomach are again assessed.

Following this, fluorescein is injected intravenously, and the perfusion of the liver and stomach are visualized using fluorescent imaging. This can be done at any point where the operation is deemed at a point of no return. There must be a small cuff of uninvolved celiac artery to allow for safe ligation. In preparation for ligation, the pancreas is divided anterior to the PV and SMV with a stapler if this has not already been done. Any involved stomach should be resected en bloc with the specimen.

19.4.3 Vascular Division

Division of the celiac axis is the last step of the operation. In addition to division of the pancreas, the splenic vein is clamped, transected, and oversewn with 5-0 polypropylene suture. This maneuver allows full visualization of the celiac trunk. A clamp is placed across the take-off at the aorta, and the celiac artery is divided and oversewn with 5-0 polypropylene sutures. Following this, the common hepatic and left gastric arteries are ligated and oversewn, again with 5-0 polypropylene suture. The specimen is removed at this point and sent for frozen section (Fig. 19.3). The stump of the pancreas is oversewn with 4-0 polypropylene sutures. Alternatively, the vessels may be transected using a stapler if there is enough room on the artery to allow for this technique.

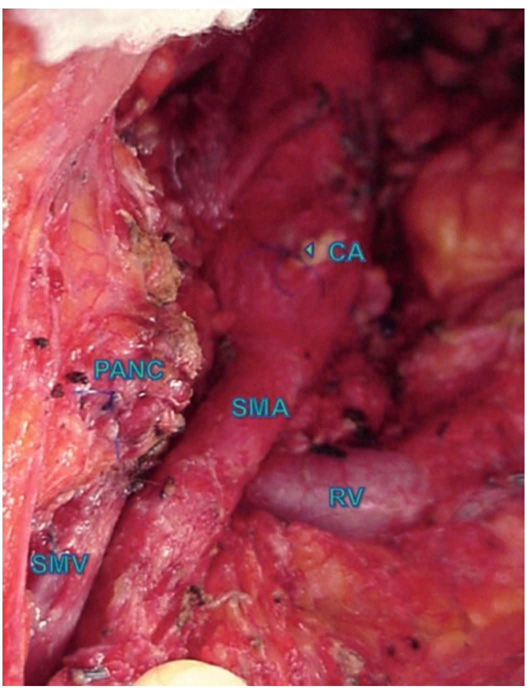

Fig. 19.3 Intraoperative images after resection. *PANC* pancreas (cut), *SMA* superior mesenteric artery, *SMV* superior mesenteric vein, *PV* portal vein, *RA* left renal vein

The blood flow to the liver and stomach are again assessed. If either structure appears ischemic, vascular reconstruction should be performed. Fluorescein may be injected again to reassess for ischemia after vascular division. Ischemia should usually be evident in the time it takes for pathologic margin assessment.

Vascular reconstruction may be done in a number of ways. Primary anastomosis between the left gastric artery or the common hepatic artery and the celiac stump is performed if mobilization of the vessels allows for a tension-free anastomosis. A reconstruction with saphenous vein graft may be preferred if a primary anastomosis is not possible. The area should be well drained to prevent pancreatic enzymes from sitting around the vascular anastomoses.

19.5 Complications

Complications associated with the modified Appleby procedure include the risks inherent to pancreatic surgery as well as risks specific to arterial resection [13]. Major complications may reach 35–41% [12–14]. The most common complication is pancreatic fistula. Nakamura et al. [13] reported a fistula rate, grade B or C, of 33%. In comparison, pancreatic fistula may be seen in up to 30% of patients undergoing distal pancreatectomy [15]. This is followed by ischemic gastropathy (29%), which in the most serious of circumstances may lead to perforation (6%). The usual result of gastric ischemia is delayed gastric emptying. Ischemia of the liver may lead to hepatic infarction and ultimately liver abscess. To minimize the risk of ischemic complications, perfusion of the liver and stomach may be assessed in two ways: (1) injection of fluorescein and (2) assessment of mean arterial pressure (MAP) from the hepatic and left gastric stumps, alth ough t his is more tedious than fluoroscein. A drop in MAP of >25% is used by some as criteria for arterial reconstruction to minimize ischemia [16]. While complications may be minimized, patients should be extensively counseled preoperatively to understand the inherent risks associated with DP-CAR.

19.6 Outcomes

Vascular resection for pancreatic adenocarcinoma was first introduced in the 1970s in the both the East and West [5, 6]. Enthusiasm from Western surgeons was initially lacking, and vascular resection fell out of favor due to high perioperative mortality. More recent institutional series have reported more favorable outcomes (Table 19.1). A meta-analysis from Mollberg et al. in 2011 reported higher perioperative mortality and worse oncologic outcomes with DP-CAR compared with DP alone [17], but more recent series in the era of neoadjuvant therapy have reported improved results [8, 9, 12, 13]. This likely reflects a refinement in the patient selection process, selecting patients who are fit and who have responded well to neoadjuvant therapy without the development of progressive and/or metastatic disease. A limitation of the meta-analysis was study heterogeneity. The evaluation included patients who were operated on over a three-decade period, with most operations performed prior to 2000, who underwent both venous and arterial resection, and included patient having undergone SMA resection and reconstruction. In contrast, the largest, single-institutional series from Nakamura and colleagues of 80 patients undergoing arterial resection reported 30-day mortality of 1.3% and in-hospital mortality of 5% [18]. The report included patients treated with and without chemotherapy both in the adjuvant and the neoadjuvant setting. The largest studies to date using neoadjuvant therapy are by Christians et al. [8] and Peters et al. [12] (Table 19.1). There were no perioperative deaths in these series of 15 and 17 patients, respectively, showing that DP-CAR can be safely performed in patients who are properly selected.

A recent analysis of data from National Surgical Quality Improvement Project (NSQIP) Pancreatectomy Demonstration Project reviewed survival across multiple treatment settings. In patients undergoing DP-CAR, mortality with celiac arterial resection was as high as 10% compared to 1% in patients undergoing DP alone [14]. While 10% mortality is not prohibitively high for an otherwise fatal condition, the high mortality in comparison to DP alone underscores the importance of performing the operation in a tertiary, multidisciplinary center. In the properly selected patient, perioperative risk may be minimized, and more aggressive surgery may be warranted in the setting of neoadjuvant chemotherapy.

Table 19.1 Reported series of modified Appleby procedure in the setting of neoadjuvant therapy

First author	Year	Number of patients undergoing AR	30-day mortality (%)	Follow-up/survival	Comments
Cesaretti [9]	2008–2013	7	0	Median survival 24 months (5 patients who underwent surgery)	7/7 (all patients also underwent CA coiling, 2 patients progressed)
Nakamura [13]	1998–2015	80	1.3 (5)[a]	Median survival 30 months	11/80 preoperative chemotherapy
Christians [8]	2011–2013	15	0	Median follow-up 21 months (9–38 months). Five recurrences, all AWD	2 patients unresectable, 14/15 preoperative chemotherapy
Peters [12]	2004–2016	17	0	Median survival 20 vs 19 months (DP-CAR vs DP, $p = 0.76$)	15/17 preoperative chemotherapy
Mollberg (meta-analysis) [17]	1974–2009	366 (12.6)[b]	0–45	Median survival 8.5–20 vs 12–25 months (DP-CAR vs DP)	Significant heterogeneity and bias

[a]Nakamura et al. report 30-day mortality of 1.3% and mortality during initial hospitalization of 5%
[b]The meta-analysis included a total of 366 patients from 26 studies, with a median of 12.6 patients per study
DP-CAR distal pancreatectomy, celiac axis resection, *DP* distal pancreatectomy, *CA* celiac axis, *AR* arterial resection, *AWD* alive with disease

Long-term survival after R0 resection with the modified Appleby procedure is improved compared with patients treated with chemotherapy alone. The median survival of patients with unresectable locally advanced disease ranges from 8.4 to 13 months [19–22]. The prognosis of patients with unresectable locally advanced pancreatic cancer is similar to patients with metastatic disease. The median survival in patients with metastatic disease treated with FOLFIRINOX chemotherapy is approximately 11 months [23]. In a study comparing gemcitabine and nab-paclitaxel to gemcitabine alone, which included patients with locally advanced disease, median overall survival for the study group was 8.5 months [24].

Long-term survival after pancreatectomy with arterial resection is similar to patients with resectable disease treated with pancreatic resection, with median survival as high as 31 months in the Japanese literature [18]. The median survival in the most recent Western series consisting of patients receiving neoadjuvant chemotherapy is between 20 and 24 months, with some data limited by short follow-up periods (Table 19.1) [8, 9, 12, 25]. In comparison, similar survival is seen in patients with resectable pancreatic cancer treated with adjuvant therapy. The ESPAC-1, CONKO-001, ESPAC-3, RTOG-9704, and GISTG trials report a median survival of 20.5–24.5 months in patients with resectable pancreatic cancer treated with or without adjuvant chemotherapy after pancreatic resection [26–30]. With multimodal treatment for locally advanced pancreatic cancer, including the modified Appleby procedure, long-term survival may be achieved in patients undergoing a margin negative resection, similar to other patients with resectable pancreatic cancer. These data suggest that patients undergoing DP-CAR do benefit oncologically from an aggressive operation despite the higher perioperative mortality.

Conclusions

Arterial resection in patients with body or tail pancreatic adenocarcinoma should be reserved for carefully selected patients with vascular involvement limited to the celiac axis or common hepatic artery. Preoperative scans should be carefully examined for collateral blood flow to the liver via the SMA and GDA. Neoadjuvant chemotherapy is advisable in all patients considered for the modified Appleby procedure (DP-CAR) with locally advanced pancreatic cancer to select those patients most likely to benefit from a major aggressive resection. With this approach, survival may be similar to patients undergoing a standard pancreatic resection.

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