11 Management of Resectable and Borderline Resectable Disease: Surgery

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Introduction

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

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History of Pancreatoduodenectomy

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

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

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

Preoperative Management

Preoperative Period: Opportunity for Optimization

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

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

Decision for Surgery

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

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

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

Operative Steps

Pancreatoduodenectomy

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

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

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

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

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

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

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

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

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

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

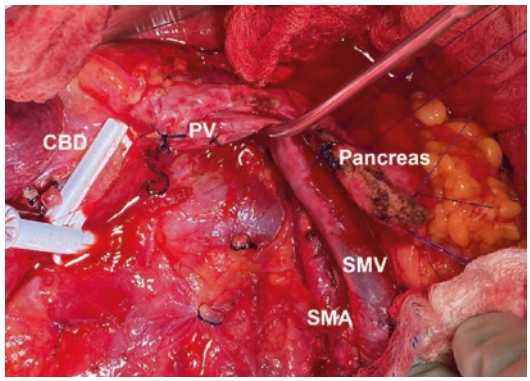

Fig. 11.1 Typical exposure of distal superior mesenteric artery (SMA) at level of J1 artery with the superior mesenteric vein (SMV) pulled to the left. Skeletonization should expose 180° of the SMA. Divided pancreas in background. Divided common bile duct (CBD) labeled

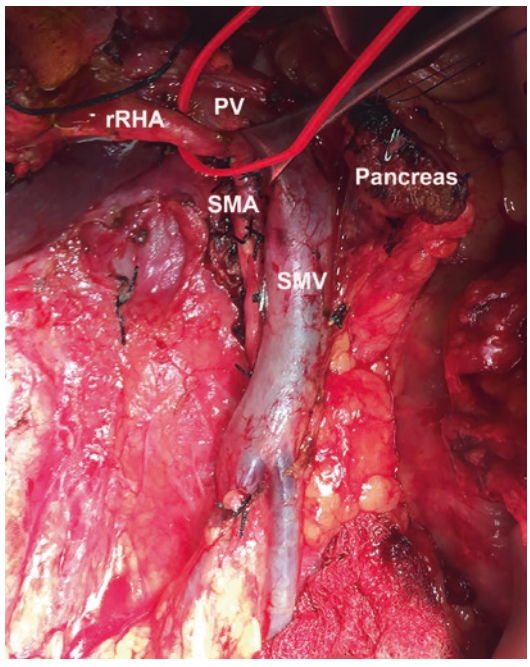

Fig. 11.2 Exposure of proximal SMA with takeoff of replaced right hepatic artery (rRHA). Superior mesenteric vein (SMV) and portal vein (PV) junction pulled to left. Note the complete skeletonization of the SMA with ties directly on pancreatic artery branches. No tissue is left on this side of the SMA

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

Considerations for Vein Involvement

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

Table 11.1 Key points of the 6-step pancreaticoduodenectomy

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

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

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

Reconstruction

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

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

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

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

Distal Pancreatectomy

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

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

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

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

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

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

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

Postoperative Management

Enhanced Recovery

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

Quality Measures

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

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

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

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

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

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

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

Future Directions

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

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