Emerging Technologies for Pancreas Resection

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ABSTRACT

Pancreatic resection has necessitated continuous technological advancements since its first introduction into the surgical field. The delicate nature and complex anatomy of the pancreas demand an evolution of techniques to improve outcomes and lessen complications. This article serves as an overview of current and emerging surgical technologies that have helped to push the bar forward, broaden candidacy, and provide patients with better quality of life postoperatively. The topics of discussion include indications for pancreatic resection, as well as traditional pancreaticoduodenectomy and distal pancreatectomy, laparoscopic and robotic resection, ctDNA biomarkers, arterial divestment and autologous grafts, near infrared surgery, irreversible electroporation, and neo-adjuvant therapies.

KEYWORDS: Pancreatic resection; pancreaticoduodenectomy; robotic pancreatic surgery; near-infrared (NIR surgery); irreversible electroporation

INTRODUCTION

The surgical complexity of pancreatic resection remains a persistent challenge when it comes to advances in safety and favorable outcomes. As pancreatic cancer continues to be a lethal threat globally with a low five-year survival rate and tendency toward late detection, it is paramount that surgical options evolve and improve. The intricacies of pancreaticoenteric reconstruction and its associated morbidity have created an ongoing pursuit to develop technologies that combine the superior exposure and dexterity granted by an open resection with the advantages of minimally invasive techniques. Here we discuss the various existing approaches to pancreatic resection along with emerging adjuncts that are aiming to fill the gap between old and new.

INDICATIONS FOR PANCREATIC RESECTIONS

Pancreatic resection has amassed a reputation over the years that can lend itself to hesitancy from both the surgeon and patient perspective. Despite major advances in surgical technique and technology, pancreatic resection is still associated with a host of probable complications both immediate and long-term, simply due to the complexity of pancreatic anatomy and the unforgiving nature of the organ. Because of this, operative intervention for pancreatic pathology is reserved for strictly appropriate candidates. Some of the current indications for resection are described below.

Pancreatic adenocarcinoma

Though not the most common gastrointestinal malignancy, pancreatic cancer maintains the highest mortality rate of all major cancers and is the fourth leading cause of cancer deaths in the United States (US). It carries an estimated 8% five-year survival rate, with an overwhelming 85% of pancreatic cancers being represented by pancreatic adenocarcinoma.[1] Moreover, there is a tendency toward late detection of pancreatic adenocarcinoma due to its asymptomatic nature in the early stages, and by the time patients are diagnosed, only about 15–20% of them have resectable disease.[2] This means that they either have metastases or major vessel involvement, making resection unsafe or impossible. For those that do have resectable disease, the mainstay of treatment includes chemotherapy ± radiation and surgery.

Pancreatic neuroendocrine tumors

A rarer malignancy making up no more than 5% of pancreatic cancers is the pancreatic neuroendocrine tumor (PNET).[3] These are neoplasms of islet cell origin that can be classified as non-functional or functional. Functional PNETs include insulinomas, gastrinomas, glucagonomas, somatostatinomas, and VIPomas. The clinical manifestations differ depending on peptide secreted, which also plays into resection indications. In general, non-functional PNETs do require resection, as they have a high chance of malignancy. Since they are often asymptomatic until they are large enough to create a mass effect, these are frequently diagnosed at a late stage. On the other hand, the resection indications for functional PNETs vary depending on the size and features of the tumors. Insulinomas and gastrinomas can be managed with enucleation if they fit a favorable size and location category, vs formal resection if otherwise. Glucagonomas, somatostatinomas, and VIPomas typically require formal resection due to high malignancy potential.[3]

Intraductal papillary mucinous neoplasm

IPMNs are a benign pancreatic lesion that are known to have malignant potential. They are cystic, mucin-producing neoplasms that grow within pancreatic ducts, and can undergo malignant transformation, making them potential precursors to pancreatic adenocarcinoma.[4] They are the most common pancreatic cystic lesion, making up about 50% of those diagnosed. Because of this, they are also the most common cystic neoplasm that undergoes resection.[5] Currently, prophylactic resection is recommended for all main duct IPMNs as well as branch duct IPMNs with high-risk features. The five-year survival rate after resection for noninvasive lesions is between 77–100%, while that of invasive carcinoma is 34–62%.[2, 6]

Serous cystadenoma/mucinous cystic neoplasms

Two other cystic neoplasms of the pancreas are serous cystadenoma and mucinous cystic neoplasms. Serous cystadenomas are reported to be the second most common pancreatic cystic lesion, followed by mucinous cystic neoplasms.[5] Since the vast majority are benign, resection is only indicated if they are greater than or equal to 4cm in size, symptomatic or obstructive, or growing on surveillance. Mucinous cystic neoplasms on the other hand, have a higher chance of malignancy, up to 25%, and resection is indicated.[5]

Chronic Pancreatitis

Patients who experience chronic pancreatitis endure a host of potentially debilitating symptoms that can extend beyond what medical management can provide. From severe abdominal pain, to ongoing fibrosis of both pancreatic tissue and adjacent organs, to impairment of endocrine and exocrine function, the wide range of manifestations can require operative intervention.[7] The most common indication for surgery in chronic pancreatitis is refractory pain due to pancreatic duct obstruction. The procedures offered typically involve resection, drainage, or a combination of both. Multiple randomized control trials have shown surgical management of chronic pancreatitis to be superior to endoscopic drainage in terms of pain relief.[8, 9] One of which demonstrated 75% of patients with partial or complete pain relief after surgery as compared to 30% after endoscopic drainage.[8]

TRADITIONAL TECHNIQUES OF PANCREATIC SURGERY: A BRIEF HISTORY

Commonly regarded as the birth of pancreatic surgery, the first successful major pancreatic resection was performed by Dr. Friedrich Trendelenburg in 1882. He performed a distal pancreatectomy for a large solid mass arising from the tail of the pancreas, and while the patient did sustain a splenic injury requiring splenectomy and died several weeks later from what was presumed to be respiratory failure, the procedure itself was technically successful and became an important landmark in the history of pancreatic surgery.[2] Several decades and daring surgeons later, Dr. Allen Whipple developed a two-stage procedure in 1935 for the radical resection of periampullary tumors which involved common bile duct ligation, cholecystogastrostomy, and posterior loop gastrojejunostomy, followed by partial duodenectomy and pancreatic head resection.[2] He later revised this and ultimately condensed it into a one-stage procedure during a 1940 case in which the patient was found intraoperatively to have a pancreatic head mass and lived for nine more years following her surgery. This technique was then refined into the pancreaticoduodenectomy, or "Whipple procedure" that we know today. Variations of this procedure are currently used for pancreatic head masses, periampullary tumors, severe pancreatic trauma, and more.

SURGICAL APPROACHES

Pancreaticoduodenectomy

The pancreaticoduodenectomy, inclusive of the classic Whipple procedure as well as pylorus sparing variations, is indicated for masses of the head of the pancreas, and bile duct and periampullary tumors. It consists of several key components, including bilioenteric reconstruction comprised of three anastomoses: pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy.[10] It is a complicated procedure that requires both careful patient selection and surgeon experience for favorable outcomes. It has been reported that the mortality of this procedure at high-volume centers is less than 1–2%, but morbidity remains high at 30–45% of patients. In patients with resectable disease, it has been shown to improve five-year mortality to about 15–25%.[11]

Distal pancreatectomy

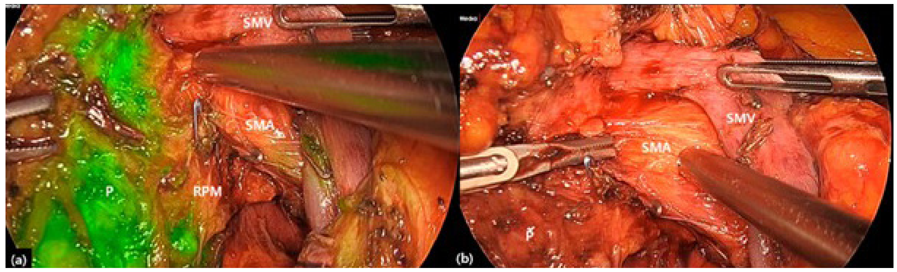
Distal pancreatectomy is indicated for tumors of the body and tail of the pancreas. Due to the anatomic proximity to the spleen, this is often performed in conjunction with a splenectomy, though a spleen-preserving variation can also be performed. Because resection of this portion of the pancreas does not require complex bilioenteric reconstruction, it is associated with a lower morbidity and mortality.

MINIMALLY INVASIVE TECHNIQUES

Laparoscopic resection

Advances in laparoscopy have been one of the most important factors in widening the candidacy for pancreatic surgery. The main advantages of laparoscopic resection over traditional open techniques include reduced intraoperative blood loss, reduced postoperative pain, and shorter length-of-stay (LOS). A meta-analysis examining six RCT on the topic of open vs minimally invasive pancreatic surgery demonstrated that the minimally invasive group had an average of 1.3 days shorter LOS, as well as 137ml less blood loss when compared to the open group.[12] This also demonstrated fewer surgical site infections. On the other hand, the same analysis revealed a longer operative time, about 54 minutes on average, for laparoscopic cases, highlighting the difficulty of the technique.[12] Overall, laparoscopic pancreatic resection has been found to be successful at high volume centers, but requires technically outstanding laparoscopists. Pancreaticoenteric anastomoses are complex surgical entities and remain a major source of morbidity even at the hands of experienced surgeons at tertiary centers.[13]

Figure 1. Intraoperative usage of ICG during pancreatic resection. The stained area is pancreatic tissue (the uncinate process), which is visually differentiated from the SMA and SMV, aiding in resection margins.[16]



Robot-assisted resection

The surgical robot solves several technical issues that traditional laparoscopy creates, from 3D visualization, to wide-ranging wrist articulation, to improved ergonomics. These advances have helped to overcome major roadblocks with laparoscopic pancreatic resection.[13] While little high powered data exists for direct comparison of laparoscopic vs robotic-assisted resection (RA), the studies we do have demonstrate the RA approach has less conversion to open surgery, and even less excessive blood loss. RA also has better oncologic outcomes with higher rates of margin negative resection and improved lymph node yield for both benign and malignant lesions.[13] However, as with any emerging technology, there is a significant learning curve to the robotic approach. This same meta-analysis also reported on the comparison of learning curve time for laparoscopic vs robotic resection, and found an average of 30 cases vs 36.5 respectively.[13]

Minimally invasive in comparison to open resection

Overall, minimally invasive techniques, whether laparoscopic or robotic, have comparable morbidity and mortality to open resection. The main advantages of open resection include a shorter operative time due to the lack of laparoscopic technical complexity, and the superior haptic feedback that open surgery provides.

EMERGING TECHNIQUES/INTRAOPERATIVE ADJUNCTS

As more surgeons are trained in minimally invasive techniques for pancreatic surgery, the next frontier to conquer is the adjunct technologies that can make these approaches even more efficient and effective. Some of these technologies are described below.

Near-Infrared (NIR) surgery

One major advantage of the minimally invasive approach to pancreatic resection is the ability to use tumor localizing dye to help guide resection. Indocyanine green (ICG) is a fluorescent dye that is given intravenously and binds to plasma proteins and remains intravascular before being cleared by hepatocytes and secreted into bile. Using an NIR camera intraoperatively after ICG administration allows for visualization of the biliary tree, various vascular structures, tumors and metastatic deposits [**Figure 1**].[14] A 2022 systematic review and meta-analysis demonstrated that the use of ICG can help surgeons identify pancreatic lesions with an accuracy of 81.3%.[14] Another study titled, *The COLPAN Study (Colour and Resect the Pancreas)* 2017, studied subjects undergoing minimally invasive resection of pancreatic neuroendocrine tumors who were injected with ICG dye to help identify lesions intraoperatively. Nine out of 10 PNETs were identified after the second bolus of ICG.[15]

Reconstructive techniques for tumors with vascular involvement

When discussing the resectability of a pancreatic tumor, an important criterion to know is the vascular involvement of the tumor. Generally speaking, if the tumor involves a major venous structure, it can still be considered borderline resectable if venous reconstruction is possible. If it has less than 180 degrees of abutment with the celiac axis or SMA, it is considered borderline resectable, and greater than 180 degrees of abutment is considered locally advanced.[17] However, development of vascular reconstructive techniques has allowed for a greater number of these tumors to be resected.

Some pancreatic tumors, particularly pancreatic ductal adenocarcinoma (PDAC), infiltrate the nerve fibers and soft tissue that surround the celiac axis, common hepatic artery, and SMA, without actually involving the arterial walls themselves.[17] This is an important distinction to make, as a true involvement of the wall requires resection, which carries a high morbidity and mortality rate. For those tumors that involve the periarterial tissue only, arterial divestment can be attempted. This is essentially a meticulous dissection of the periadventitial plane between the tumor and the artery itself, allowing for an R0 resection without needing to do any resection or reconstruction [**Figure 2**].[18]

Graft reconstruction

For those tumors that do have true involvement beyond the adventitia of these major arterial structures, surgeons have

Figure 2: Sub-adventitial divestment of a grade I tumor with invasion into the tunica adventitia.[19]

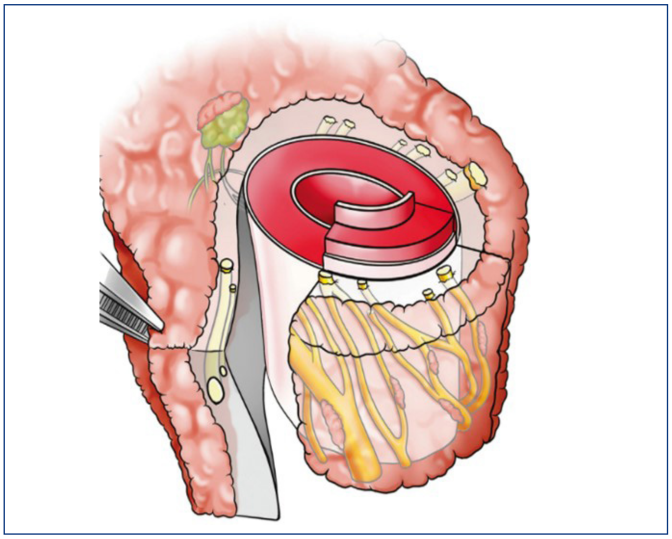
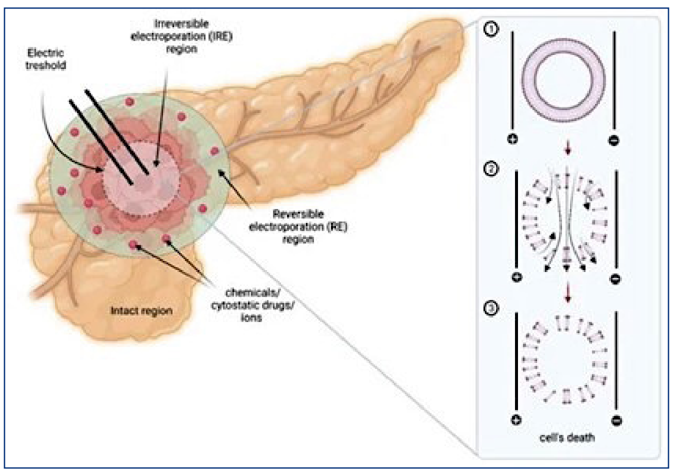


Figure 3: Irreversible electroporation electrodes surrounding pancreatic tumor.[23]



the option of using autologous or synthetic grafts to reconstruct the vessels that require resection. In certain cases with short segment involvement, end-to-end anastomosis can be performed, but most patients undergoing arterial resection will require an interposition graft. Several autologous options exist, including harvested saphenous or renal veins, or splenic artery if splenectomy is also being performed.[17] Synthetic grafts can also be used, though care must be taken in these cases to avoid graft infection.[17] Though these techniques have evolved and improved over the years, arterial resection and reconstruction remain significant sources of morbidity and mortality in pancreatic resections, with one study citing a 90-day major morbidity rate of 53% and mortality rate of 14%.[20] Most of these complications were due to postoperative hemorrhage, pancreatic fistula, or ischemia.[20]

Irreversible electroporation (IRE)

So far, our discussion has focused primarily on operative strategies for resectable disease. However, a significant subsect of patients have unresectable disease without arterial reconstruction options. One treatment modality under development for these patients is irreversible electroporation (IRE). This strategy involves an ablation technique that uses high voltage, low energy electropulsations to create pores in the tumor cell membranes, leading to necrosis [**Figure 3**]. Because this is a non-thermal technique, there is no risk of thermal injury to surrounding areas, making it a theoretically safe approach for tumors close to vital structures.[21] This technique is particularly useful for margin accentuation, or the treatment of tumor edges in order to decrease the likelihood of leaving positive tumor margins behind.[22] The efficacy of this technique has been demonstrated in vivo and in vitro studies. While the technology is promising, one major disadvantage of IRE is its inability to eradicate larger tumors >3cm. This is potentially due to the fact that the electrodes would need to be further away from the core of the target tissue, leading to a decreased magnitude of pulsation reaching each part of the mass.[22] Regardless of this, IRE remains an exciting territory for treatment of pancreatic malignancies, even if only as an adjunct to surgical resection.

FUTURE DIRECTIONS

Despite all of the impressive advancements discussed above, the final frontier of successful treatment of pancreatic cancer is early detection of disease. Currently, the majority of pancreatic cancers are discovered only after symptoms have manifested and disease is more likely to be at least locally advanced at that time. Some sources estimate up to 85% of diagnosed PDACs are locally advanced or metastatic at the time of diagnosis.[20]

An emerging area of interest for early detection is the "liquid biopsy" or body fluid sample such as blood, saliva, or urine, that may contain biomarkers that can direct a diagnosis of pancreatic cancer. One such biomarker being examined is circulating cell-free tumor DNA (ctDNA). This approach looks for circulating nucleic acids of tumor cells that are prevalent during early stage disease, which could provide diagnosis without the undue risk of tissue biopsy.[20] While the concept is promising for future development, ctDNA testing is currently somewhat controversial as a method for early detection of pancreatic cancer due to its instability, low circulating volume, and variable sensitivity and specificity across available studies.[20]

Another encouraging area undergoing development is neoadjuvant chemotherapy for pancreatic cancer. Currently, some data supports that a course of neoadjuvant chemotherapy can improve 12-month overall survival rates to 77% compared to 40% in the upfront surgery groups.[24] This data also shows that it can make patients with previously unresectable cancers newly eligible for surgery, as well as improve the overall survival of those who experience postoperative complications.[24]

CONCLUSION

As new technologies emerge to help solve problems in the operating room, an additional problem is created: where do these technologies fit in with existing techniques and how can they be incorporated to improve outcomes as well as efficiency? The advent of the surgical robot has moved the needle forward dramatically in terms of creating a more ergonomic operating environment with improved visualization without needing to commit patients to the complications associated with open surgery; however, we continue to seek out additional tools that can be used along with the robot that can push it to be unequivocally superior for safety and outcomes. The adjuncts discussed here have indeed broadened surgical candidacy and therefore allowed more patients to lead longer and more comfortable lives, which is the ultimate purpose of this work.

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Disclosures

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