Current surgical management of pancreatic cancer

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ABSTRACT	En bloc resection is the treatment of choice for localized pancreatic cancer. While the perioperative mortality associated with resection is low, it still carries a significant morbidity rate of up to 50% in certain high-risk subsets of patients. With advances in perioperative care, radical resection with inclusion of adjacent vascular structure to achieve negative margin status can be performed with comparable mortality and morbidity in high-volume centers. Early results with the use of minimally invasive technique in pancreatic surgery are promising. Recent data on perioperative care to decrease morbidity with pancreatic surgery will also be discussed.
KEY WORDS	pancreaticodoudenectomy; distal pancreatectomy; laparoscopic pancreatic surgery

Introduction

Worldwide, over 200,000 people die annually of pancreatic cancer. In the United States, pancreatic cancer is the 4th leading cause of cancer death, and in Europe it is the 6th (1). Great majority of patients present with locally advanced or metastatic disease (2). Surgical resection remains the only potentially curative intervention for select patients who present with localized disease. In 1912, Walter Kausch reported the first successful resection of duodenum and a portion of the pancreas for periampullary tumor (3). In 1935 Whipple redefined the procedure as a two stage operation consisting of gastric and biliary bypass in the first stage followed by pancreaticoduodenectomy (4,5). In 1978, Traverso and Longmire introduced the pylorus preserving pancreaticoduodenectomy (6). During the 1960s, many centers reported operative mortality following pancreaticoduodenectomy to be 20-40%, with postoperative morbidity at 40-60% (7). With advances in surgical techniques and perioperative care, the mortality rates associated with the procedure has reduced to less than 5%, while morbidity rate approached 40% even in high-

volume centers (8-11).

Approximately 15-20% of patients initially diagnosed with pancreatic caner are amenable to resection (12,13). Great majority of pancreatic cancer (90%) are ductal in origin located predominantly in the head (>75%) (14). Unresectable lesions are those involving SMA or celiac axis (T4) or those with distant metastases (M1). Controversy exists regarding the definition of borderline resectable lesions. Generally, tumor abutment of visceral arteries or short-segment occlusion of the superior mesenteric vein is considered anatomically borderline resectable lesion (15). Recent Consensus Conference sponsored by Americas HepatoPancreatoBiliary Association, Society for the Surgery of Alimentary Tract, and Society of Surgical Oncology provided a more precise definition for clinical trial design and literature comparison (16) : (i) tumor-associated deformity of the superior mesenteric vein (SMV) or portal vein (PV) (Figure 1); (ii) abutment of the SMV or PV $\geq 180^0$; (iii) short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction; (iv) short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction (Figure 2); and (v) abutment of the superior mesenteric artery ($<180^0$). Outcome following resection is influenced by R0 resection (10,11,17), nodal involvement (10,11), histologic grade (11,18), elevated CA19-9 levels (18-20), high Body Mass Index (21), and operative blood loss (17,22).

Operative techniques for head of pancreas cancer include the standard pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy. Extended retroperitoneal lymphadenectomy and superior mesenteric vein and/

Figure 1 Arrow points toward the deformity of superior mesenteric vein by tumor.

Figure 2 Arrow points toward the deformity of portal vein and abutment of tumor on the common hepatic artery.

or portal vein resection have recently been evaluated for maximal surgical clearance of disease. The type of pancreatic anastomosis has also been examined, including pancreaticojejunostomy versus pancreaticogastrostomy. Several institutions have reported their results for laparoscopic pancreatic resection with comparable results to open resection. Various post operative strategies have been evaluated for reduction of post-operative complication rates, including the use of octreotide (somatostatin analogue) , pancreatic enzyme replacement therapy, erythromycin and nutritional support The purpose of this article is to review the preoperative, operative, and post operative management strategies in the treatment of pancreatic cancer.

Determination of resectability
Paramount to the decision for performing pancreaticoduodenectomy is the accurate identification of patients who have resectable disease. Various imaging modalities are available to accurately stage a patient with pancreatic cancer, including CT, PET/CT, ERCP, endoscopic ultrasound, mesenteric angiography, and MRCP. CT scan has been the main imaging modality for determination of resectability. With advances in medical imaging and improvement in the resolution capability, the role of diagnostic laparoscopy is now limited in the initial evaluation of resectability. In a recent study of 298 patients, Mayo et al reported 87% resection rate in this cohort where CT was performed in 98% of the study patients, EUS in 32%, and laparoscopy in 29% (23). In the laparoscopy group, 27% had findings that precluded resection. In a recent review of their experience at Memorial Sloan-Kettering Cancer Center, White et al reported an yield
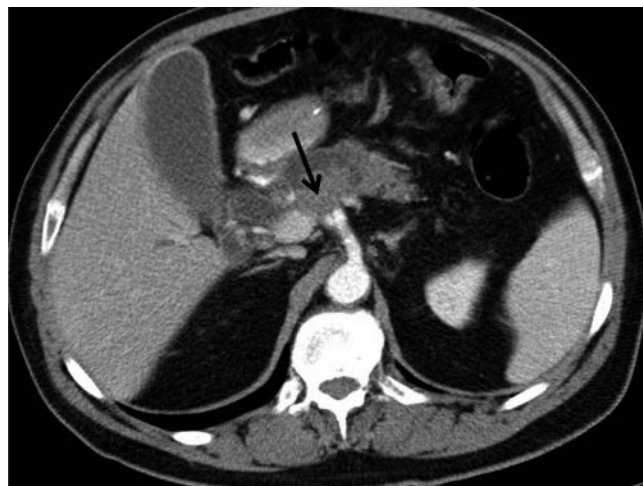
of diagnostic laparoscopy of 14% overall, but only with 8% yield in patients with in-house pre-operative imaging versus 17% with external imaging (24). The same group proposed a judicious use of diagnostic laparoscopy with the combination of pre-operative CA19-9 as a stratification factor to consider laparoscopy in those with resectable disease on imaging and elevated CA19-9 level (25).

Preoperative Biliary Drainage
Because of the predominant location of pancreatic cancer in the head of pancreas, obtructive jaundice is a common presenting symptom. Several cohort studies have been published regarding the detrimental effect of pre-operative biliary instrumentation/stenting on the post-operative course with higher infectious complications in the stented group (26-31). No difference in survival was observed. However, others have reported no impact on post-operative complications with pre-operative biliary drainage (32,33) In a recent multicenter randomized trial comparing early surgery versus preoperative biliary drainage followed by surgery, 202 patients were enrolled. The rates of serious complications were 39% (37 of 96 patients) in the early-surgery group and 74% (75 of 106 patients) in the biliary-drainage group (P<0.001) (34). A follow-up report from the same trial showed that there was a significant delay in time to surgery (1 week versus 5 week). However, the delay did not influence survival (35). While there is an increase in overall infectious complications following surgery in the stented group, the detrimental effect of pre-operative biliary stenting is likely limited to those with subsequent bacterial colonization of the biliary tree from stent placement (36). Jagannath et al found no difference in post-operative

128

Kim et al. Current surgical management of pancreatic cancer

complications between the un-complicated pre-operative stent group compared with unstented group. The adverse outcome was associated with positive intraoperative bile culture. Further adding to the controversy of pre-operative biliary stenting, while high pre-operative bilirubin was associated with worse survival outcome, resolution of jaundice following pre-operative biliary stenting appeared to counter the adverse survival effect of bilirubinemia (37). Thus, pre-operative biliary drainage should be used judiciously in symptomatic patients.

Operative considerations

Pancreaticoduodenectomy

The traditional pancreaticoduodenectomy (PD) consists of resection of the pancreatic head, duodenum, distal common bile duct, gallbladder, and gastric antrum (4,5). A more recent modification of this procedure involves preservation of the pylorus and gastric antrum, referred to as the pylorus preserving pancreaticoduodenectomy (PPPD)(6). Resection is then followed by re-establishing gastrointestinal continuity. The jejunum is typically used for each anastomosis, consisting of pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy or duodenojejunostomy in the case of PPPD. During the 1960s and 1970s, mortality associated with PD approached 25%. Over the past 3 decades, experience performing PD has increased with associated decrease in perioperative mortality rate to less than 5% (38-41). However, it is still a technically challenging procedure with significant perioperative morbidity. Cameron reported his personal series of 1000 PD performed over a span of 34 years with 1% perioperative mortality (41). Perioperative morbidity was observed in 41% of the cohort including delayed gastric emptying (18%), pancreatic fistula (12%), wound infection (7%), intra-abdominal abscess (6%), cardiac event (3%), pancreatitis (2%), bile leak (2%), pneumonia (2%), hemobilia (2%), and reoperation in 2.7%. To minimize post-operative morbidity, various strategies for reconstruction have been under intense investigation. The predominant controversy regarding standard PD versus PPPD or pancreaticojejunostomy versus pancreaticogastrostomy reconstruction has been extensively studied (42-44). No significant superiority of one variant of PD over another has been convincingly demonstrated. Surgeon's experience with the specific variant of PD appeared to be the determining factor in achieving optimal surgical outcome.

Distal pancreatectomy

Distal pancreatectomy is the standard procedure for cancer of the body or tail of pancreas. It entails the resection of distal portion of pancreas extending from the left of the superior mesenteric vein / portal vein axis to the tail with en bloc resection of surrounding lymphatic tissue. Spleen is conventionally removed with the procedure. Spleen-sparing distal pancreatectomy (Warshaw operation) can be performed safely without increase in complication rate, operative time or in-hospital stay (45). While cancer of the body and tail tends to present at an advanced stage due to the lack of early symptoms and tends not to be amenable to complete resection on presentation, there is no survival difference when compared with cancer of the head of pancreas stage by stage (46,47).

Laparoscopic pancreatic resection

With the publication of COST trial, minimally invasive surgical approach has been evaluated in increasing frequency for cancer resection (48). For the surgical management of pancreatic neoplasm, laparoscopic distal pancreatectomy (LDP) is rapidly becoming the surgical procedure of choice in place of open distal pancreatectomy (ODP) for tumor of the body/tail of pancreas. While several groups have published their results with LDP, the majority of the publication did not specifically address the oncologic outcome following LDP for pancreatic cancer (49-59). Overall, when compared with ODP, LDP is associated with a longer operative time, less blood loss, and shorter length of stay. Conversion rate from laparoscopic approach to open varies between 0 to 30%. In their institutional experience, Baker et al noted a lower number of lymph nodes harvested in 27 LDP patients (mean=5) compared with 85 ODP patients (mean=9) (57). Kooby et al performed a matched analysis of 23 LDP patients with 189 ODP patients from a database with pooled data from 9 academic centers (58). There was no difference in positive margin rates, number of lymph nodes examined, or overall survival in patients with pancreatic cancer. Jayaraman et al reviewed their results of 343 distal pancreatectomies over a 7-year study period at Memorial Sloan-Kettering Cancer Center : 107 were attempted laparoscopically and 236 ODP (59). The conversion rate was 30%. Similar complication rates were observed in both groups. They also observed significantly less blood loss, longer operative times, and shorter hospital stays in favor of LDP group. The number of lymph nodes examined (LDP = 7 vs. ODP = 7) and margin positivity (LDP = 3% vs ODP = 4%) were similar between both groups. They observed a higher conversion rate in patients with larger tumor, higher BMI, and tumor proximity to celiac axis. No survival data were provided. Based on these data, LDP appeared to be an appropriate oncologic surgical approach in select patients with cancer of the body/tail of pancreas.

Table 1 Select Literature on Laparoscopic PD

	N	Conversion rate (%)	Mean OR Time (min)	Mean Blood Loss (ml)	Mean Length of Stay (d)	Overall Morbidity (%)	Mortality (%)	Positive Margins (%)
Gagner (61)	10	40	510	NR	22	50	0	0
Dulucq (62)	25	12	287	107	16	32	4	0
Palanivelu (63)	42	0	370	65	10	NR	2	0
Pugliese (64)	19	32	461	180	18	37	0	0
Cho (65)	15	0	338	445	16	27	0	0
Kendrick (66)	62	0	368	240	7	42	2	11

Laparoscopic pancreaticoduodenectomy (LPD) was first described by Gagner and Pomp in 1994 (60). Due to the complexity of the operation and lack of apparent advantages, reports regarding LPD contained case reports and small series. Series containing 10 or more successful LPD are listed in Table 1. While these reports demonstrated the safety and feasibility of performing LPD, larger prospective trials are needed to further define the advantage, if any, of LPD.

Role of extended retroperitoneal lymphadenectomy

Nodal status is a significant prognostic variable in pancreatic cancer. The number of nodes involved with metastases, the ratio of lymph node involvement, and the minimum number of lymph nodes examined had all been shown to have prognostic significance (67-69). Because of the importance of nodal staging, extended lymphadenectomy (EL) during pancreaticoduodenectomy was proposed to improve the surgical outcome of pancreatic cancer patients. The definition of EL is not uniform. Commonly EL referred to the dissection of additional lymph nodes along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to the renal hila with circumferential clearance of the celiac trunk (70). While several groups from Japan had reported favorable outcome following EL during pancreaticoduodenectomy (71-73), multiple randomized trials had not demonstrated an improvement in overall survival following EL (70,74-76). Yeo et al also observed a significantly higher complication rate associated with the radical surgery group (43%) compared with the standard pancreaticoduodenectomy group (29%) (74). Higher rates of delayed gastric emptying and pancreatic fistula and longer hospital stay were observed in the radical surgery group. The higher morbidity associated with EL was also reported in a meta-analysis on standard versus radical pancreaticoduodenectomy (77). The authors also did not find a difference in survival between the standard versus radical pancreaticoduodenectomy.

Portal vein and superior mesenteric vein resection

Because achieving an R0 resection had prognostic significance for patient outcome, vascular resection during PD had been evaluated. The great majority of vascular resection during PD involved portal vein and superior mesenteric vein resection and reconstruction. Yekebes et al reported equivalent perioperative morbidity and mortality between the standard PD group and the group with vascular resection (78). The median survival was 15 months in patients with histopathologic proven vascular invasion and 16 months in those without (P=0.86). Riedeger and colleagues also reported similar results with regard to portal vein/superior mesenteric vein resection (79). In their study cohort of 222 pancreaticoduodenectomy patients, 53 required portal vein and/or superior mesenteric vein resection while 169 did not. There was no significant difference in morbidity or mortality between the two groups. Kanoeka and colleagues demonstrated that the length of portal vein / superior mesenteric vein (PV/SMV) resected had an inverse correlation with survival (80). PV/SMV resections that are < 3 cm were associated with a 5-year survival rate of 39% vs. 4% for resections that are ≥3cm in length (P=0.017). Chua and Saxena performed a systematic review of published reports on extended pancreaticoduodenectomy with vascular resection (81). Twenty-eight retrospective studies were included in the review comprising of 1458 patients. The median R0 resection rate was 75% (range, 14%-100%). The median mortality rate was 4% (range, 0-17%). Based on the reports from high-volume centers (>20 pancreaticoduodenectomy/year), the median survival associated with extended pancreaticoduodenectomy with vascular resection was 15 months (range, 9-23 months). Therefore, in select patient where R0 resection can be achieved, PV/SMV resection/reconstruction can be performed with comparable morbidity and survival outcome to standard

130

Kim et al. Current surgical management of pancreatic cancer

pancreaticoduodenectomy.

Post operative considerations

While the perioperative mortality for pancreaticoduodenectomy has dropped to 5% in recent times due to advances in surgical techniques, the morbidity rate remains high at 40%. Pancreatic fistula remains the most serious complication after pancreaticoduodenectomy and occurs in up to 20% of patients. Other major complications include delayed gastric emptying and hemorrhage. In an effort to identify independent risk factors for post operative morbidity, Adam and colleagues prospectively studied 301 patients who underwent pancreatic head resections (82). Three pre-operative risk factors were found to independently correlate with increased complication rate: presence of portal vein/splenic vein thrombosis or hypertension, elevated pre-operative creatinine, and the absence of pre-operative biliary drainage. In contrast, other studies (including a prospective randomized controlled trial) have reported a statistically significant higher complication rate for patients undergoing pre-operative biliary drainage (26-31,34). Patients undergoing operation after 1998 were also noted to have fewer complications, suggesting that increased experience and improved patient selection has led to improvement in perioperative care. The requirement for resection of additional organs also correlated with a higher complication rate.

Patient's age and its impact on morbidity, mortality, and survival have been intensely investigated (83-87). The majority of studies used age 70 or 80 as the cutoff. In their systematic review of literature, Riall et al found that higher morbidity and/or mortality was observed in the elderly population (87). Makary et al reviewed their single institutional experience with 2,698 patients undergoing pancreaticoduodenectomy over a 35 year period (83). When compared to the younger group (<80), patients in the 80-89 group had statistically significant higher morbidity and mortality rates (p<0.05). Haigh et al identified 2610 patients undergoing pancreaticoduodenectomy from 1/2005 through 12/2007 in the American College of Surgeons-National Surgical Quality Improvement Program database (88). Elderly patients (>70 years old) had a higher likelihood of developing at least 1 morbidity compared with that of younger patients (40.7% vs 34.0%; P = .01). Furthermore, elderly patients had a higher perioperative mortality rate compared with that of younger patients (4.3% vs 1.7%; P = .01).

The efficacy of octreotide, a somatostatin analogoue, in decreasing complication associated with pancreatic resection is controversial. The rationale for using octreotide is that it can decrease pancreatic enzyme secretion thereby decreasing the rate of pancreatic fistula formation (89). Multiple randomized multicenter trials comparing octreotide or vaprotide, another somatostatin analogue, to placebo in patients undergoing pancreatic resection have been performed (89-97). The use of somatostatin analogues did not impact mortality in patients undergoing pancreatic resection. While some studies demonstrated a statistically significant decrease in the development of pancreatic leak/fistula with the use of somatostatin analogue, others showed no difference.

Delayed gastric emptying is another leading cause of morbidity in patients undergoing pancreaticoduodenectomy (98). The occurrence of delayed gastric emptying resulted in prolonged nasogastric tube decompression, initiation of enteral or parenteral nutrition, and prolonged hospital stay. The pathogenesis of delayed gastric emptying has been attributed to decrease gastric motility secondary to decreased levels of motilin (99). Motilin induces contractions of intestinal smooth muscles, initiates phase III of the gastric migrating motor complex, and improves gastric emptying in patients with diabetic gastroparesis (100,101). Yeo and colleagues performed a prospective randomized trial evaluating the effects of erythromycin on delayed gastric emptying in patients undergoing pancreaticoduodenectomy, randomizing 118 patients to erythromycin lactobionate 200 mg every 6 hours or saline. The erythromycin group had reduced incidence of delayed gastric emptying (19% vs. 30%), need for nasogastric tube re-insertion (6 vs 15 patients, p<0.05), and retention of liquids and solids on radionucleotide gastric emptying study (p<0.01) (102). Thus, the use of erythromycin can reduce the occurrence of delayed gastric emptying after pancreaticoduodenectomy.

Patients with pancreatic cancer who are deemed candidates for curative resection are frequently malnourished pre-operatively (103,104). Serum albumin level is a significant prognostic indicator of post operative mortality. Winter and colleagues categorized patients into 3 groups based on pre-operative serum albumin level (>3.5, 2.6-3.5, <2.6). Post operative mortality was 7% in the group with lowest serum albumin level compared with 3% for the intermediate group, and 0.9% for the >3.5 group (105). Okabayashi and colleagues evaluated the benefit of early post operative enteral nutrition (EPEN) vs. late post operative enteral nutrition (LPEN) in patients undergoing pancreaticoduodenectomy (106). Twenty-three patients received TPN followed by the initiation of oral intake during the late post operative period (LPEN group). Sixteen patients were initiated on enteral feeds via jejunostomy tube on post-

operative day 1 (EPEN group). The EPEN group had significantly lower rate of post-operative pancreatic fistula and shorter length of hospital stay. Brennan and colleagues performed a prospective randomized trial in patients undergoing major pancreatic resection, comparing patients receiving parenteral nutrition with patients who did not (107). They found that the group receiving parenteral nutrition had significantly higher complication rate with increased rate of intra-abdominal infection and longer duration of hospitalizaion.

Continuous infusion of nutrients has been demonstrated to cause a delay in gastric emptying. Elevated levels of cholecystokinin (CCK) is a known cause of delayed gastric emptying (108,109). Van Berge Henegouwen and others performed a prospective randomized study comparing continuous (CON) feeding protocol (1500 kCal/24hrs) with cyclic (CYC) feeding protocol (1125 kCal/18hr) (110). They found that patients in the CYC group were able to tolerate a normal diet sooner than the CON group. The length of hospital stay was shorter in the CYC group. Levels of CCK were lower in the CYC group, suggesting that lower levels of CCK plays a role in reducing delayed gastric emptying.

Enteral nutrition formulas containing immunomodulating agents (arginine, RNA, Omega-3 fatty acids) have been investigated in patients undergoing cancer surgery. Braga and colleagues performed a prospective randomized double blind clinical trial comparing standard enteral feeds with enteral feeds enriched with arginine, RNA, and Omega-3 fatty acids post operatively in patients undergoing curative resection for neoplasms of the colorectum, stomach, or pancreas (111). Patients receiving immunomodulating agents had a statistically significant decrease in post operative infection rate and length of post operative stay. The use of probiotics has been shown to stabilize the intestinal barrier, increase intestinal motility, and enhance the innate immune system. Rayes and colleagues performed a randomized double blind study in 80 patients undergoing pylorus preserving pancreaticoduodenectomy. One group received early post-operative enteral feeds with lactobacillus, and the other group received placebo (112). The incidence of post operative infections was significantly lower in the group receiving lactobacillus compared with placebo group(12.5% vs. 40% p=0.005).

Conclusion

While resection of pancreatic cancer can be performed with low perioperative mortality, the associated perioperative morbidity can be significant. Recent advances in surgical instrumentation have made wide spread adoption of laparoscopic distal pancreatectomy possible. Similar to experience in other cancer types, the initial oncologic outcome with laparoscopic distal pancreatectomy appear comparable to open distal pancreatectomy. The advantage of minimally invasive surgery in terms of less blood loss and shorter hospital stay was also observed. The advances in surgical techniques also allow more aggressive surgical resection to be performed with acceptable perioperative mortality and morbidity. With the advances in systemic treatment of pancreatic cancer, the ability to achieve negative resection margin will improve the outcome of patients with this aggressive disease.

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