Review Article

Laparoscopic Staging and Surgical Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer is the tenth most common cancer and the fourth leading cause of cancer deaths in the United States. Surgery remains a cornerstone in the treatment of pancreatic cancer. Unfortunately, the percentage of patients presenting at the resectable stage is minimal. Although computed tomography (CT) scan remains the best modality to stage the tumor for resectability, laparoscopy and laparoscopic ultrasound offers its own advantages. Extended lymphadenectomy, portal vein resection, and arterial reconstruction have also been explored in multiple studies to enhance staging. The traditional pancreaticoduodenectomy (Whipple's procedure) with regional lymphadenectomy is still the standard of care in the surgical treatment of pancreatic cancer.

Keywords: Laparoscopy, Pancreatic cancer, Staging, Surgery

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Introduction

Pancreatic ductal adenocarcinoma is the tenth most common cancer diagnosis in the United States. It represents the fourth most common cause of cancer deaths, with nearly 40,000 deaths reported in 2010.[1]

Although surgery is the main therapeutic modality for pancreatic cancer, only 10-20% of patients are eligible for resection at the time of presentation.[2] We searched Medline from 1940 to 2011 using the keywords pancreatic cancer and staging, surgery, management, treatment, and laparoscopy. The information contained in our review was synthesized from other review articles, guidelines from Gastroenterology societies and original articles.

Laparoscopic Staging

Contrast enhanced computed tomography (CT) is the preferred test for cancer staging. However, laparoscopic examination of pancreatic tumors allows direct visualization and along with laparoscopic ultrasound (LUS), it can reveal intra-parenchymal liver metastases, tiny peritoneal metastases, and vascular invasiveness of the tumor giving us a clearer picture of the resectability of the cancer.

In recent years, laparoscopic staging has been a major advance in the staging of pancreatic and periampullary tumors.[3-7] In patients who appear to have a resectable cancer on a helical CT, 20-30% have undetected local spread or hepatic or peritoneal implants, which prevent curative resection.[8] As new modalities for nonoperative palliation, such as biliary stenting are now available, a formal laparotomy is frequently not needed. In such cases laparoscopic staging may help to avoid laparotomy in advanced disease and minimize the morbidity. Simple laparoscopy allows sampling of visceral and peritoneal surfaces, which would detect otherwise undetectable metastasis. Staging laparosocopy with frozen section evaluation of the biopsy specimens can be followed by a formal laparotomy for tumor removal using the same anesthesia. This method reduces unresectable disease at laparotomy by up to 50% in some studies.[5,7]

Diagnostic laparoscopy with the use of ultrasound improves the accuracy of predicting resectability up to as high as 98% in some studies.[9]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.106183

Bemelman, *et al*. studied 70 patients with pancreatic cancer with laparoscopy and LUS. In this staging study, 21 patients had metastatic disease. In addition, out of 49 patients undergoing laparotomy, 21 of 22 considered resectable after LUS examination were resected; 6 of 13 patients that were considered "probably resectable" as well as 2 of 14 that were initially considered unresectable, were, in fact, resected. The overall sensitivity and specificity for determining resectability was 67% and 96%, respectively. In this study unnecessary laparotomy was avoided in 14 patients (19%) and a surgical decision was changed in 18 patients (25%) using laparoscopy and LUS.[10]

The use of Doppler flow techniques now allows us to identify vascular encasement or occlusion as well.[4,5] Conlon, *et al*. conducted further in-depth laparoscopic staging by examining the celiac, periportal, and peripancreatic lymph nodes.[6] Laparoscopic peritoneal washings are also subjected to cytological analysis to determine patients with disseminated disease.[3] Unfortunately as these procedures are time consuming, they extend operative time and may also necessitate two surgical procedures, one for staging and one for resection, which increases costs and patient morbidity.

In some studies, the accuracy of laparoscopy in combination with LUS for assessing resectability approaches that of open laparotomy without significantly increasing morbidity or mortality. As with other ultrasound techniques, LUS is limited by observer variation. Selective use of laparoscopy with LUS for staging in questionable unresectable cases seems to be rational.

Surgery in Pancreatic Cancer

The surgical approach depends on the location of the tumor and adjacent invasion. Patients with pancreatic cancer may be classified as resectable, locally advanced, and metastatic. Recently a few patients have been classified as borderline resectable as well.

Tumors that are potentially resectable are defined as those that have not encased the portal and superior mesenteric veins and not invaded the roots of the celiac or superior mesenteric arteries. Such resection is the best option for disease free survival. Most resectable tumors are those of the pancreatic head and the procedure of choice is a pancreaticoduodenectomy (PD) (Whipple's procedure).

Pancreaticoduodenectomy

PD was first started in the United States by Allen O. Whipple in 1935 as a two stage procedure; the first operation involves a cholecysto-gastrostomy, followed 3-4 weeks later by resection of the stomach, pancreas, and duodenum. Dr. Whipple described a one stage PD in 1941.[11,12] Whipple's surgery involves resection of the head of the pancreas, distal bile duct, most of the duodenum and proximal jejunum. The procedure is very demanding and requires precise dissection around portal and mesenteric vessels as well as three distinct anastomoses. In the mid-1970s, mortality and morbidity was so high that a palliative bypass was considered a preferred procedure.[13-15] Since that time, a steep reduction in perioperative mortality with PD has been noted.[16] Postoperative mortality has dropped from 20% to less than 5% at some centers.

In a large single-institution study, Winter, *et al*. evaluated the outcomes of 1175 patients who had PD for pancreatic ductal adenocarcinoma from 1970 to 2006. The operating time was 380 minutes with a median blood loss of 800 ml. Perioperative mortality was 2% and morbidity stood at 38%. The average length of stay was 9 days, and median survival time was 18 months.[17]

Near-zero mortality, which is defined as less than 2%,[8] is being reported in many 100+ patient case series. One reason for the decline could be concentration of procedures at high volume centers.[18-21] This can be seen from the fact that low volume centers still have a mortality of 15-20% in national surveys.[20,21] Data from Maryland, New York, and the national Medicare database showed a 3- to 5-fold increase in mortality at low-volume centers (defined by fewer than five cases per year) compared with centers that do 20 or more cases. The experience of the operating surgeon has also been correlated to low postoperative mortality.[21] The decrease in mortality at high volume centers parallels a decrease in mortality of other surgical procedures as well as improvements in intensive care, diagnostic and interventional radiology, and nutritional support. Improved prophylaxis and management of infection, gastrointestinal hemorrhage, and venous thromboembolism are other potential causes. Thus, postoperative cardiopulmonary complications and gastrointestinal hemorrhage that were very common in the past have sharply reduced. In addition, disruption of the pancreatico-jejunal anastomosis, which was a common cause of death, now rarely leads to death.[22]

Wagner, *et al.* observed a significant difference between patients who had R1 resections (median survival, 11.5 months) and R0 resections (median survival, 20.1 months) and concluded that R0 resection is a significant independent predictor of long-term survival.[23]

However, not all studies found resection margin to be a significant factor for survival.[24]

Morbidity with PD

Although mortality has decreased, morbidity after PD still has major morbidity. Improvements in surgery have reduced leakage at the biliary-enteric anastomoses to less than 5%.[16] In contrast, leakage at the pancreaticoenteric anastomoses still occurs in 10-20% of cases.[16] This is the weak point of the operation and leakage is most common when the pancreatic duct is small and the gland is very soft.[8] As per current reports leakage at the pancreaticojejunostomy leads only to an increased length of stay and rarely to reoperation or death.[22]

The most common postoperative complication of PD is delayed gastric emptying, probably due to disruption of enterogastric signaling after duodenectomy. Once it was thought that this was more common in patients undergoing pylorus preservation.[25] More recent evidence shows that the rate of this complication is equally high in Classic Whipple's with hemigastrectomy.[26] This complication is seen in nearly 20% of cases and ranges from mild nausea to persistent vomiting requiring nasogastric suction. It is rarely life threatening but leads to a prolonged hospital stay. A randomized prospective trial of erythromycin showed a modest but statistically significant improvement in gastric emptying post PD, probably due to its effect on motilin receptors.[27]

Long-Term Survival with PD

Five-year survival after Whipple's for ampullary, bile duct and duodenal cancer has always ranged between 30% and 50% in most series and resection of a mucinous tumor of the pancreas results in more than 75% survival at 5 years.[8] In contrast, the long-term survival for pancreatic adenocarcinoma has been very dismal. A literature review of articles around the world over the past 50 years has shown a 5 year survival of 4% post-curative resection.[28] Unfortunately, some of these patients noticed a recurrence beyond 5 years suggesting no cure of their disease. Recently though, large case series from high volume centers have shown that better long-term results to the tune of 20%, 5-year survival are possible with documented pancreatic adenocarcinoma.[29-31] With disease free resection margins, no lymph node metastases and small tumors, 40% of patients may survive to the 5-year mark. Not all recent series have shown this improvement though and this should be remembered. Possible causes for improvement may be improvements in diagnosis, surgical technique, and the use of adjuvant chemo-radiotherapy.

Pylorus Preservation

Pylorus preserving pancreaticoduodenectomy (PPPD) was first described by Dr. Watson in 1944.[32]

Traverso and Longmire further stimulated the interest in PPPD where the entire stomach, pylorus as well as 3-6 cm of duodenum is preserved and a duodenojejunal anastomoses is made. The purpose of this operation is to reduce complications of hemigastrectomy-dumping, marginal ulceration, and bile reflux gastritis.[33] Studies have confirmed preservation of pylorus function and decreases in dumping and enterogastric reflux.[34] Other surgeons point to the fact that in the era of H2 histamine receptor blockers and proton pump inhibitors, marginal ulceration is uncommon. In addition, they feel that delayed gastric emptying is more common in pylorus preservation,[25] although this is not supported by randomized studies.[26] The adequacy of this operation as a cancer operation has not been proven, although data has shown no difference in morbidity, mortality, and long-term survival between this and hemigastrectomy.[35]

Pancreaticoduodenectomy vs Pylorus Preserving Pancreaticoduodenectomy

There was always a controversy over the benefits of PPPD versus PD. There were a number of studies comparing PD with PPPD. A Cochrane review included all randomized, controlled trials between March 2006 and January 2011 with a total of 465 cases and found no differences in morbidity, mortality, and survival for patients receiving PPPD or PD. Contrary to the perceived benefits of preserving the duodenum, the bulk of the literature shows no difference in outcomes after PPPD was compared with PD.[36]

Classic Whipple's vs Total Pancreatectomy

Classic Whipple's with preservation of pancreatic body and tail was considered inferior to total pancreatectomy by some. Total pancreatectomy was thought to offer more extensive resection for extensive and multifocal disease and potentially removed more involved peripancreatic lymph nodes.[37,38] In addition, this procedure did not need a pancreaticoenteric anastomoses.

It was found that the development of diabetes, which was brittle and hard to control, was universal with total pancreatectomy. In addition, pancreatic cancer was rarely found to be multifocal[39] and this type of surgery did not remove a greater number of lymph nodes that a periampullary tumor metastasized to.[40] In addition, pancreaticoenteric anastomoses leaks now rarely lead to death.[22,41] Thus total pancreatectomy is now only done in cases where the tumor has spread to the body and tail.

Distal Pancreatectomy

The surgical standard of care for pancreatic cancers of

the body and tail of the pancreas is distal pancreatectomy (DP) and splenectomy. Dr. Bilroth first introduced distal pancreatic resection in 1884. Patients with pancreatic body or tail masses do not become symptomatic until their disease frequently has reached an unresectable stage. Long-term outcomes after attempted resection are poor as well.[42,43]

Sperti, *et al*.[44] reported on 24 patients who underwent DP for adenocarcinoma of the body and tail of the pancreas with no adjuvant radiotherapy or chemotherapy. They observed a morbidity of 25% and a mortality rate of 8%. The 5 year survival rate for these patients was 12.5%, which was similar to rates reported for survival after PD for pancreatic head cancer.

The patients who will benefit the most from DP are those with neuroendocrine or mucinous tumors where cure rates postresection are high.

Regional Pancreatectomy

Fortner's group at Memorial Sloan-Kettering Cancer Center championed an extensive operation for cancers in the pancreatic head and named it regional pancreatectomy.[45] This operation involved a total or subtotal pancreatectomy and resection and reconstruction of the superior mesenteric vein-portal vein-confluence and an extensive en bloc regional lymph node dissection.[46] Fortner's experience in 56 patients demonstrated a high major morbidity and 30-day mortality of greater than 5%.[46] Of the ones who survived more than 30 days, some succumbed to surgical complications after a 30-day or greater postoperative hospitalization. Long-term survival was connected to tumor size. Five year survival for a tumor with a diameter <2.5 cm was 33%, for a size 2.5-5 cm it was 12%, and for size >5 cm it was 0%. These figures were not better than the classic Whipple's, but morbidity and mortality was greater.[47] Sindelar showed similar findings of greater morbidity and mortality with this procedure compared with traditional Whipple's surgery.[48] Sindelar also found occurrence of loco-regional spread and distant metastases with this radical operation, thus disproving the theory that this extra dissection would provide better control of tumor spread.[49] The main legacy of regional pancreatectomy is that two of its principles – portal vein resection and extensive lymph node removal have survived.

Subtotal Stomach-Preserving pancreaticoduodenectomy

Subtotal stomach-preserving PD aims to preserve as much stomach as possible while minimizing problems related to delayed gastric emptying that are associated with preserving the pyloric ring in the face of a loss of vagal innervations.[50,51] In this procedure, the duodenum, pylorus, and 1-2 cm of stomach are resected with the pancreatic specimen and the jejunal anastomosis fashioned to the distal antrum. One study compared the incidence of delayed gastric emptying after this operation with standard or pylorus-preserving PD.[51] Although the rate was marginally less compared with a pylorus-preserving operation, there was no difference from conventional PD. The incidence of ulceration may be higher than with conventional PD (due to retained antrum producing large amounts of gastrin), but no improvements in median survival or disease-free survival have been demonstrated with this procedure. Some surgeons feel that by not performing antrectomy, the yield of lymph nodes in the resected specimen is reduced, thus altering the stage of disease.

Portal Vein Resection

In some instances, the evidence of portal vein involvement or superior mesenteric vein involvement is obvious intra-operatively. In many studies, tumor involvement of the portal vein has been associated with a very poor outcome.[52,53] One reason could be that tumors that involve the portal vein are ones that are biologically more aggressive or it could be that the portal vein is involved purely due to anatomic location of the primary tumor and if such a tumor undergoes margin-negative resection a very good outcome could be obtained.

Hence, the question arises whether resection of the portal vein along with PD will improve outcomes.

Results from a study of 110 patients from the M.D. Anderson Cancer Center and the Memorial Sloan-Kettering Cancer Center suggest that patients undergoing portal vein resection have a similar morbidity and mortality compared with those having a standard PD. The median survival was about 2 years in both the cohorts.[54]

Analysis of resected specimens also showed that tumors that involve the portal vein did not have a greater chance of aneuploidy or a likelihood of being node positive compared with tumors that do not. Thus, they are not biologically more aggressive but rather this is an unfortunate anatomic result.[55]

Interestingly not all patients with portal vein invasion have true histologic invasion by the tumor. In many cases, peri-tumoral inflammation mimics tumor invasion. The rates of histologically confirmed vein invasion found in the literature range from 52% to 78%.[56-58] Nakagohri, *et al*. found only 52% of patients who underwent PD with portal vein resection had invasion on histology.[59]

When comparing patients that have portal vein resection with histologic portal vein invasion to those having resection with negative histology, a higher rate of positive margins and poorer prognosis was seen in the former. Thereby, the significance of achieving negative margins with PD and portal vein resection was evident in many studies.[60,61]

A study done at the University Of Pennsylvania concluded that in patients with portal vein involvement that is otherwise resectable with tumor negative margins, en bloc resection should be done.[8]

The major reason for a tumor not being resectable is circumferential involvement of the portal and superior mesenteric vein and occlusion of the portal vein with resulting mesenteric vein hypertension. Tumors encasing the portal vein often also invade the superior mesenteric artery. Many high volume centers do not perform PD if preoperative staging shows encasement of the portal or superior mesenteric vein.[8,55,62] However, the recent classification includes a borderline resectable stage where vessel encasement is less than 180°.

PD in conjunction with portal vein resection is now accepted therapy in many specialized centers, with equivalent outcomes when compared with PD alone It is obvious from all these studies that PD with portal vein resection does not lead to improved survival over PD alone. However, it helps in making the tumor amenable to complete resection. Thereby, these patients who are now able to undergo complete resection of their tumor have significantly improved survival compared with patients with unresectable disease.

Extended Lymphadenectomy

The regional lymph nodes usually resected with the PD include anterior and posterior pancreaticoduodenal nodes. Periampullary malignancies may metastasize to lymph nodes beyond the limits of standard Whipple's.[40] In order to remove regional nodes before distant spread many investigators proposed a wide lymph node resection from the celiac axis to the iliac bifurcation, along with portal-mesenteric lymph nodes.[63,64] The Japanese who aggressively adopted this technique, demonstrated better results compared with historical controls or contemporary populations undergoing standard PD.[65,66]

Extended lymphadenectomy included removal of lymph nodes from the hilum of the liver and along the aorta from the diaphragm to the inferior mesenteric artery, laterally to both hila of the kidneys and circumferential clearance of the nodes along the celiac trunk and superior mesenteric artery.

There are at least three prospective, randomized, controlled trials that have been published by Pedrazolli, *et al.*, Farnell, *et al.*, and Yeo, *et al.*, which looked at the utility of performing PD in conjunction with extended lymphadenectomy.[64,67,68]

A formal meta analyses reached the same conclusion[69] as did a prospective randomized controlled trial at Johns Hopkins Hospital.[64]

Therefore current evidence does not support extending lymphadenectomy with PD compared with traditional regional lymphadenectomy for the treatment of pancreatic cancer.

Arterial Resection/Reconstruction

Locally advanced tumors include tumors, which invade or encase the arterial vasculature, including the hepatic artery, celiac trunk, or superior mesenteric artery. Encasement of less than 180° is considered borderline resectable by some surgeons. Nakao, *et al.* studied an arterial resection of the celiac artery in 3 patients, the hepatic artery in 9 patients, and the superior mesenteric artery in 3 patients undergoing PD, total pancreatectomy, or DP. They observed a 1-month mortality rate of 35.7% in the above scenarios.[70] Takahashi, *et al.* in a study of 16 patients observed a mortality rate of 44%.[71]

Studies by Yekebas, *et al.* and Stitzenberg, *et al.* have shown improved survival with arterial resection.[72,73]

Thus, although some studies seem to show improved survival in these select patients compared with palliative measures, arterial invasion still remains a contraindication to surgical intervention in the majority of patients.

Pancreaticojejunostomy vs Pancreaticogastrostomy

In most series, the three leading causes of morbidity after PD are delayed gastric emptying, wound infection, and pancreatic fistula resulting from a pancreatic anastomotic leak.[22,74-78] Failure of a pancreatic-enteric anastomosis to heal after PD can be a source of considerable morbidity and can contribute to mortality. The incidence of pancreatic anastomotic leak ranges from 5% to 25% in most series. Because pancreatic fistula has been such a common problem after PD, various techniques of managing the pancreatic remnant (body and tail of the pancreas) have been studied.[79] A re-popularized option for enteric drainage of the pancreatic remnant is pancreatico-gastrostomy. Reported results of pancreatico-gastrostomy have been favorable, with low rates of pancreatic fistula and mortality.[80-82]

A prospective randomized clinical trial found that pancreatic fistula is a common complication after PD, with an incidence most strongly associated with surgical volume and underlying disease, but their data did not support the hypothesis that pancreatico-gastrostomy is safer than pancreaticojejunostomy or is associated with a lower incidence of pancreatic fistula.[41]

Pancreaticoenteric Anastomosis

Leakage at pancreaticoenteric anastomosis was reported to double postoperative hospitalization in a large patient series.[41] There are two main types of anastomoses done – intususcepting and duct to mucosa. Pancreatic fistula formation rates using either techniques have been found to be equivalent.[8] Recently, several studies have championed a meticulous duct to mucosa anastomis, where the cut edges of the pancreatic duct are anastomosed to the intestinal mucosa through a small opening in the jejunum, under loupe magnification with fine absorbable sutures to reduce pancreatic fistula development to less than 5%.[83-85] Some studies have looked at using somastatin analogues such as octreotide to reduce pancreatic fistulae. Unfortunately, several randomized trials of octreotide use in Whipple's for prevention of pancreatic fistulae have shown no benefit.[86,87]

Adjuvant and Neoadjuvant Chemotherapy

As previously seen, surgical therapy has only modest success in pancreatic cancer and chemoradiotherapy has been pursued to reduce local and regional recurrence postsurgery. The classic study for chemoradiotherapy in pancreatic cancer was done by the Gastrointestinal tumor study group (GITSG).

It prospectively randomized patients undergoing curative resection to no additional therapy or combined bolus 5-fluorouracil (5-FU) and external beam radiation therapy. Despite small numbers, a significant survival difference was seen with those in the additional therapy arm surviving 20 months vs 11 months in the resection only group.[88] GITSG confirmed this in a subsequent trial.[89]

An initial report by the European Organization for the Research and Treatment of Cancer (EORTC) showed no benefit of adjuvant chemoradiotherapy, but a recent reanalysis showed 14% increased overall survival at 2 years (37% vs 23%), which was statistically significant (P = 0.049) and thus supported adjuvant chemoradiotherapy for pancreatic head cancers.[90] A distinct multi-institutional study, European Study Group for Pancreatic Cancer-One (ESPAC-1), which was criticized for methodological shortcomings showed benefit only with 5-FU but not with adjuvant radiotherapy.[2]

A population-based study of the Surveillance, Epidemiology, and End Results (SEER) registry with 2636 patients records from 1973 to 2003 (1123 received adjuvant radiation therapy and 1513 did not) was conducted to determine the survival benefit of adjuvant radiotherapy.[91] After a 19-month follow up, median survival was 18 months vs 11 months favoring the adjuvant radiation group. (P < 0.01). In addition, Cox regression analysis showed a statistically significant survival benefit (Hazard ratio 0.57 (95% confidence interval [CI] 0.52-0.63), P < 0.01).[91]

A recent phase III European trial demonstrated survival benefit of single agent gemcitabine adjuvant therapy with median disease free survival times of 13.4 months vs 6.9 months in control (P < 0.001).[92] A single-institution phase II chemo-radiation adjuvant therapy study by Picozzi, *et al*. in Seattle, using a combination of 5-FU, *cis*-platinum, and interferon-α as radiation sensitizers, showed a drastic improvement in median survival time and 5-year survival rate (longer than 36 months and approximately 50%, respectively) in a cohort of patients after surgical resection.[93] If the above results are confirmed by a multi-institutional phase II trial of the American College Of Surgeons Oncology group, then it will be a dramatic advance in the future of pancreatic cancer therapy.

Recently several groups have suggested preoperative neoadjuvant therapy for periampullary tumors.[94,95] An advantage of this approach is shrinkage of primary, so that surgical resection is easier. In addition, those who will not receive postoperative adjuvant therapy due to complications will at least receive preoperative therapy. Such therapy may also decrease tumor dissemination at surgery. Although the feasibility and safety of neoadjuvant therapy has been clinically demonstrated and efficacy is also considered encouraging in phase II studies,[96,97] this therapy is currently considered experimental. Although this will change in the future, for current practice adjuvant chemoradiotherapy may be considered for patients who are undergoing curative resection if no clinical trials are available.

Summary

The current accepted practice for staging is dynamic contrast enhanced CT scan and laparoscopy with LUS may be indicated for a selected group of patients who are not clearly defined by CT scan. The preferred surgical modality in pancreatic cancer is PD or PPPD. There is no evidence that PPPD is better than PD. R0 resections with negative margins with traditional regional lymphadenectomy is the standard of care.

The extended lymphadeectomy does not offer major advantage over the typical regional lymph node removal. Though portal vein resection does not offer any benefit in outcome, it helps many patients who were initially classified as unresectable to get surgical treatment and make it obvious that portal vein involvement is not an absolute contraindication for surgery. Fewer studies showed increased survival with arterial resection and reconstruction, but with high mortality rates, and therefore, is not a recommended approach. We did not discuss the use of neoadjuvant chemotherapy, which is beyond the scope of this review.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
2. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, *et al.* A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-10.
3. Warshaw AL. Implications of peritoneal cytology for staging of early pancreatic cancer. Am J Surg 1991;161:26-9.
4. John TG, Greig JD, Carter DC, Garden OJ. Carcinoma of the pancreatic head and periampul-lary region: Tumor staging with laparoscopy and laparoscopic ultrasound. Ann Surg 1995;221:165-70.
5. Callery MP, Strasberg SM, Doherty GM, Soper NJ, Norton JA. Staging laparoscopy with laparoscopic ultrasonography: Optimizing resectability in hepatobiliary and pancreatic malignancy. J Am Coll Surg 1997;185:33-9.
6. Conlon KC, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 1996;223:134-40.
7. Vollmer CM, Drebin JA, Middleton WD, Teefey SA, Linehan DC, Soper NJ, *et al.* Utility of staging laparoscopy in subsets of peripancreatic and biliary malignancies. Ann Surg 2002;235:1-7.
8. Drebin JA, Metz JM, Furth EE. Carcinoma of the Pancreas. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, Gillies McKenna M, editors. Abeloff's Clinical Oncology, 4th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2008. p. 1595-608.
9. Pisters PW, Lee JE, Vauthey JN, Charnsangavej C, Evans DB. Laparoscopy in the staging of pancreatic cancer. Br J Surg 2001;88:325-37.
10. Bemelman WA, de Wit LT, van Delden OM, Smits NJ, Obertop H, Rauws EJ, *et al.* Diagnostic laparoscopy combined with laparoscopic ultrasonography in staging of cancer of the pancreatic head region. Br J Surg 1995;82:820-4.
11. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102:763-76.
12. Trimble IR, Sherman CP. A one- stage operation for the cure of carcinoma of the ampulla of Vater and head of the pancreas. Surg Gynecol Obstet 1941;73:711-22.
13. Shapiro TM. Adenocarcinoma of the pancreas: A statistical analysis of bypass vs. Whipple resection in good risk patients. Ann Surg 1975;182:715-21.
14. Crile G Jr. The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. Surg Gynecol Obstet 1970;130:1049-53.
15. Hertzberg J. Pancreatico-duodenal resection and by-pass operation in patients with carcinoma of the head of the pancreas, ampulla, and distal end of the common duct. Acta Chir Scand 1974;140:523-7.
16. Strasberg SM, Drebin JA, Soper NJ. Evolution and current status of the Whipple procedure: An update for gastroenterologists. Gastroenterology 1997;113:983-94.
17. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, *et al.* 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10:1199-210.
18. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43-9.
19. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638-45.
20. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, *et al.* Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-37.
21. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL, *et al.* Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117-27.
22. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: Incidence, significance and management. Am J Surg 1994;168:295-8.
23. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586-94.
24. Butturini G, Stocken DD, Wente MN, Jeekel H, Klinkenbijl JH, Bakkevold KE, *et al.* Influence of resection margins and treatment on survival in patients with pancreatic cancer: Meta-analysis of randomized controlled trials. Arch Surg 2008;143:75-83.
25. Warshaw AL, Torchiana DL. Delayed gastric emptying after pylorus preserving pancreaticoduodenectomy. Surg Gynecol Obstet 1985;160:1-4.
26. Stojadinovic A, Hoos A, Brennan MF, Conlon KC. Randomized clinical trials in pancreatic cancer. Surg Oncol Clin N Am 2002;11:207-29.
27. Yeo CJ, Barry MK, Sauter PK, Sostre S, Lillemoe KD, Pitt HA, *et al.* Erythromycin accelerates gastric emptying after pancreatico: Duodenectomy. Ann Surg 1993;218:229-38.
28. Gudjonsson B. Carcinoma of the pancreas: Critical analysis of costs, results of resections, and the need for standardized reporting. J Am Coll Surg 1995;181:483-503.
29. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduoden- ectomies. Ann Surg 2006;244:10-5.
30. Kevork KK, Hines OJ, Eibl G, Reber HA. Management of pancreatic fistulas after pancreaticoduodenectomy: Results in 437 consecutive patients. Arch Surg 2005;140:849-55.
31. Janes RH Jr, Niederhuber JE, Chmiel JS, Winchester DP, Ocwieja KC, Karnell JH, *et al.* National patterns of care for pancreatic cancer. Results of a survey by the Commission on Cancer. Ann Surg 1996;223:261-72.
32. Watson K. Carcinoma of the ampulla of Vater. Successful radical resection. Br J Surg 1994;31:368-73.
33. Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978;146:959-62.

34. Williamson RC, Bliouras N, Cooper MJ, Davies ER. Gastric emptying and enterogastric reflux after conservative and conventional pancreatoduodenectomy. Surgery 1993;114:82-6.
35. Drebin JA, Strasberg SM. Carcinoma of the pancreas and tumors of the periampullary region. In: Winchester DP, J.R., Murphy GP, editors. Cancer Surgery for the General Surgeon, Philadelphia: Lippincott Williams and Wilkins; 1999. p. 195-211.
36. Diener MK, Heukaeufer C, Schwarzer G, Seiler CM, Antes G, Knaebel HP, *et al.* WITHDRAWN: Pancreaticoduodenectomy (classic Whipple) versus pylorus-preserving pancreaticoduodenectomy (pp Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev 2011;16:CD006053.
37. van Heerden JA, McIlrath DC, Ilstrup DM, Weiland LH. Total pancreatectomy for ductal adenocarcinoma of the pancreas: An update. World J Surg 1998;12:658-62.
38. Brooks JR, Brooks DC, Levine JD. Total pancreatectomy for ductal cell carcinoma of the pancreas. An update. Ann Surg 1989;209:405-10.
39. Klöppel G, Lohse T, Bosslet K, Rückert K. Ductal adenocarcinoma of the head of the pancreas: Incidence of tumor involvement beyond the Whipple resection line. Histological and immunocytochemical analysis of 37 total pancreatectomy specimens. Pancreas 1987:2:170-5.
40. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the pancreas area. Cancer 1978;41:880-7.
41. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, *et al.* A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580-8.
42. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;223:506-11.
43. Nordback IH, Hruban RH, Boitnott JK, Pitt HA, Cameron JL. Carcinoma of the body and tail of the pancreas. Am J Surg 1992;164:26-31.
44 Sperti C, Beltrame V, Bellamio B, Pasquali C. Spleen-preserving distal pancreatectomy with splenic vessels excision. Surg. 2012;152:140-1.
45. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Ann Surg 1984;199:418-25.
46. Fortner JG, Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. Ann Surg 1996;223:147-53.
47. Yang JM, Southern JF, Warshaw AL, Lewandrowski KB. Proliferation tissue polypeptide antigen distinguishes malignant mucinous cystadenocarcinomas from benign cystic tumors and pseudocysts. Am J Surg 1996;171:126-9.
48. Sindelar WF. Clinical experience with regional pancreatectomy for adenocarcinoma of the pancreas. Arch Surg 1989;124:127-32.
49. Johnstone PA, Sindelar WF. Patterns of disease recurrence following definitive therapy of adenocarcinoma of the pancreas using surgery and adjuvant radiotherapy: Correlations of a clinical trial. Int J Radiat Oncol Biol Phys 1993;27:831-4.
50. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, *et al.* Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection-long term results. Br J Surg 2005;92:547-56.
51. Fujii T, Kanda M, Kodera Y, Nagai S, Sahin TT, Hayashi M, *et al.* Preservation of the pyloric ring has little value in surgery for pancreatic head cancer: A comparative study comparing three surgical procedures. Ann Surg Oncol 2012;19:176-83.
52. Cameron JL, Crist DW, Sitzmann JV, Hruban RH, Boitnott JK, Seidler AJ, *et al.* Factors influencing survival after pancreaticoduo- denectomy for pancreatic cancer. Am J Surg 1991;161:120-5.
53. Furukawa H, Kosuge T, Mukai K, Iwata R, Kanai Y, Shimada K, *et al.* Helical computed tomography in the diagnosis of portal vein invasion by pancreatic head carcinoma. Arch Surg 1998;133:61-5.
54. Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, *et al.* Pancreaticoduodenectomy with vascular resection: Margin status and survival duration. J Gastrointest Surg 2004;8:935-49.
55. Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, *et al.* Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric–portal vein confluence. Ann Surg 1996;223:154-62.
56. Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, *et al.* Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154-62.
57. Riediger H, Makowiec F, Fischer E, Adam U, Hopt UT. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. J Gastrointest Surg 2006;10:1106-15.
58. Muller SA, Hartel M, Mehrabi A, Welsch T, Martin DJ, Hinz U, *et al.* Vascular resection in pancreatic cancer surgery: Survival determinants. J Gastrointest Surg 2009;13:784-92.
59. Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003;186:149-53.
60. Bachellier P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD, *et al.* Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 2001;182:120-9.
61. Nakao A, Takeda S, Sakai M, Kaneko T, Inoue S, Sugimoto H, *et al.* Extended radical resection versus standard resection for pancreatic cancer: The rationale for extended radical resection. Pancreas 2004;28:289-92.
62. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? Ann Surg 1996;224:342-7.
63. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, *et al.* Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Ann Surg 1998;228:508-17.
64. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, *et al.* Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: Randomized controlled trial evaluating survival, morbidity and mortality. Ann Surg 2002;236:355-66.
65. McFadden DW, Reber HA. Cancer of the pancreas: Radical resection—supporting view. Adv Surg 1994;27:257-72.
66. Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, *et al.* Practical usefulness of lymphatic and connective tissue clearance for carcinoma of the head of the pancreas. Ann Surg 1988;208:215-20.
67. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P,

Pasquali C, *et al.* Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: A multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508-17.

68. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, *et al.* A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138:618-28.
69. Michalski CW, Kleeff J, Wente MN, Diener MK, Büchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreatico- duodenectomy for pancreatic cancer. Br J Surg 2007;94:265-73.
70. Nakao A, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, *et al.* Indications and techniques of extended resection for pancreatic cancer. World J Surg 2006;30:976-82.
71. Takahashi S, Ogata Y, Tsuzuki T. Combined resection of the pancreas and portal vein for pancreatic cancer. Br J Surg 1994;81:1190-3.
72. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, *et al.* En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: Perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247:300-9.
73. Stitzenberg KB, Watson JC, Roberts A, Kagan SA, Cohen SJ, Konski AA, *et al.* Survival after pancreatectomy with major arterial resection and reconstruction. Ann Surg Oncol 2008;15:1399-406.
74. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217:430-5.
75. Miedema BW, Sarr MG, van Heerden JA, Nagorney DM, McIlrath DC, Ilstrup D. Complications following pancreaticoduodenectomy. Current management. Arch Surg 1992;127:945-9.
76. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988;207:39-47.
77. Yeo CJ, Barry MK, Sauter PK, Sostre S, Lillemoe KD, Pitt HA, *et al.* Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. Ann J Surg 1993;218:229-37.
78. Grace PA, Pitt HA, Tompkins RK, DenBesten L, Longmire WP Jr. Decreased morbidity and mortality after pancreatoduodenectomy. Ann J Surg 1986;151:141-9.
79. Madiba TE, Thomson SR. Restoration of continuity following pancreaticoduodenectomy. Br J Surg 1995;82:158-65.
80. Delcore R, Thomas JH, Pierce GE, Hermreck AS. Pancreatogastrostomy: A safe drainage procedure after pancreatoduodenectomy. Surgery 1990;108:641-5.
81. Kapur BM. Pancreaticogastrostomy in pancreaticoduodenal resection for ampullary carcinoma: Experience in thirty-one cases. Surgery 1986;100:489-93.
82. Mason GR, Freeark RJ. Current experience with pancreatogastrostomy. Am J Surg 1995;169:217-9.
83. Howard JM. Pancreatojejunostomy: Leakage is a preventable complication of the Whipple resection. J Am Coll Surg 1997;184:454-7.
84. Strasberg SM, Drebin JA, Mokadam NA, Green DW, Jones KL, Ehlers JP, *et al.* Prospective trial of a blood supply-based technique of pancreaticojejunostomy: Effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194:746-60.
85. Peng S, Mou Y, Cai X, Peng C. Binding pancreaticojejunostomy is a new technique to minimize leakage. Am J Surg 2002;183:283-5.
86. Lowy AM, Lee JE, Pisters PW, Davidson BS, Fenoglio CJ, Stanford P, *et al.* Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997;632-41.
87. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, *et al.* Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419-29.
88. Kalser MH, Ellenberg SS. Pancreatic cancer: Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899-903.
89. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer 1987;59:2006-10.
90. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, *et al.* Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: Phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-84.
91. Greco JA, Feurer ID. Survival benefit with adjuvant radiation therapy in surgically resected pancreatic cancer. In Gastroenterointestinal Cancer Symposium Proceedings; 2007. p. 140.
92. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, *et al.* Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA 2007;297:267-77.
93. Picozzi VJ, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am J Surg 2003;185:476-80.
94. Spitz FR, Abbruzzese JL, Lee JE, Pisters PW, Lowy AM, Fenoglio CJ, *et al.* Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15:928-37.
95. Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB 3rd. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: An Eastern Cooperative Oncology Group study. J Clin Oncol 1997;16:317-23.
96. Talamonti MS, Small W Jr, Mulcahy MF, Wayne JD, Attaluri V, Colletti LM, *et al.* A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol 2006;13:150-8.
97. Cheng TY, Sheth K, White RR, Ueno T, Hung CF, Clary BM, *et al.* Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. Ann Surg Oncol 2006;13:66-74.

How to cite this article: Muniraj T, Barve P. Laparoscopic staging and surgical treatment of pancreatic cancer. North Am J Med Sci 2013;5:1-9.

Source of Support: Nil. **Conflict of Interest:** None declared.