Nontherapeutic Celiotomy Incidence Is Not Affected by Volume of Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

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Nontherapeutic celiotomy for pancreatic adenocarcinoma is detrimental to patients by delaying medical treatment as a result of unnecessarily incurred postoperative recovery time. This study was undertaken to evaluate whether surgeon volume of pancreaticoduodenectomy for pancreatic adenocarcinoma impacted the incidence of nontherapeutic celiotomy. All patients undergoing an intended pancreaticoduodenectomy for pancreatic adenocarcinoma were evaluated from 2003 to 2012. Survival was calculated using Kaplan-Meier analysis. The association between surgeon volume of pancreaticoduodenectomy and occurrence of nontherapeutic celiotomy was assessed using Fisher's exact test. Median data are presented. Eight surgeons undertook 443 intended pancreaticoduodenectomies for patients with pancreatic adenocarcinoma; 329 (74%) patients underwent pancreaticoduodenectomy, whereas 114 (26%) patients underwent nontherapeutic celiotomies. Two surgeons undertook 85 per cent of operations. Surgeon volume did not impact the incidence of nontherapeutic celiotomies ($P = 0.26$). Seventy-seven (68%) patients had metastatic disease at the time of the operation, whereas 37 (32%) patients had locally advanced unresectable disease. These patients had survivals of 5.0 and 6.0 months, respectively ($P = 0.77$). A high proportion of patients—one in four—undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma will ultimately undergo a nontherapeutic celiotomy. Surgeon volume of pancreaticoduodenectomy for pancreatic adenocarcinoma does not lessen the incidence of nontherapeutic celiotomies. Preoperative prediction of patients with imaging-occult metastatic or locally advanced disease remains a challenge, even for high-volume surgeons. Attempts to create algorithms for patients with high risk of imaging-occult metastatic or locally advanced disease to undergo staging laparoscopy and/or positron emission tomography scanning may decrease the burden of patients undergoing nontherapeutic celiotomies.

PATIENTS WITH PANCREATIC adenocarcinoma continue to have dismal survival. Pancreatic cancer is the fourth leading cause of cancer death in the United States and has the highest fatality rate worldwide.[1, 2] The overwhelming majority (approximately 80%) of patients with pancreatic adenocarcinoma have locally advanced, unresectable, and/or metastatic disease that precludes resection.[3–5] Complete tumor resection for pancreatic cancer continues to be the only hope for cure and has been shown to significantly improve survival.[6] Medical therapy for pancreatic cancer is at best adjunctive to tumor resection.

Nontherapeutic celiotomy for pancreatic adenocarcinoma is detrimental to patients by presenting risk without benefit and by delaying medical treatment and any palliation it might offer as a result of unnecessarily incurred postoperative recovery time. Staging laparoscopy, to date, has not been shown to significantly benefit patients with suspected pancreatic adenocarcinoma.[7, 8] This study was undertaken to determine the incidence of nontherapeutic celiotomy for patients undergoing an intended pancreaticoduodenectomy, define risk factors for nontherapeutic celiotomy, and evaluate whether surgeon volume of pancreaticoduodenectomy for pancreatic adenocarcinoma impacted the incidence of nontherapeutic celiotomy.[9] We hypothesized that surgeon volume of pancreaticoduodenectomy would directly

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correlate with the incidence of nontherapeutic celiotomy for patients with pancreatic adenocarcinoma.

Methods

Data Management

All patients undergoing an intended pancreaticoduodenectomy for pancreatic adenocarcinoma were evaluated from 2003 to 2012. Patients were entered into this database with Institutional Review Board approval after giving informed consent. Data were stored in Microsoft Excel (Microsoft Corp., Redmond, WA) files. Statistical analysis used Graphpad Instat Version 3.06 and Graphpad Prism 5 (Graphpad Software Inc., San Diego, CA). Survival curve analyses were also undertaken on Graphpad Prism 5, which permitted the log rank and Wilcoxon tests on the Kaplan-Meier survival curves. Associations with nontherapeutic celiotomy were determined using Fisher's exact test. When appropriate, data are presented as median, mean ± standard deviation. Significance was accepted when the P value was < 0.05.

Preoperative Evaluation

Preoperatively, patients underwent staging with an oral/intravenous contrasted, triple-phase, computed tomography with thin cuts through the pancreas. Patients underwent endoscopic ultrasonography evaluation when additional characterization of the mass was warranted or a biopsy was needed. Biopsies were not routinely obtained from pancreatic masses. Endoscopic retrograde cholangiopancreatography with stenting was undertaken when biliary decompression before surgical intervention was necessary as a result of cholangitis and to improve comorbidities in preparation for surgical resection. Patients with resectable pancreatic masses with potential for complete tumor extirpation with no evidence of distant metastasis were taken to the operating room. Unresectable tumors at celiotomy were determined from the following criteria: 1) the presence of extrapancreatic disease beyond the extent of a pancreaticoduodenectomy; 2) tumor encasement (greater than 180° circumference) of the celiac axis, common hepatic artery, or superior mesenteric artery; and 3) portal vein and superior mesenteric vein thrombosis or occlusion from tumor invasion.[6]

Results

Intended pancreaticoduodenectomy was undertaken by eight surgeons for 443 patients with pancreatic adenocarcinoma, 52 per cent men and 48 per cent woman, with a median age of 67 (67 ± 9.8) years old. Pancreaticoduodenectomy was successfully undertaken for 329 (74%) patients, whereas 114 (26%) patients underwent nontherapeutic celiotomies. Twenty-two of the 114 nontherapeutic celiotomies underwent palliative bypasses (19 gastroenterostomies, three choledochoenterostomies). The majority of patients who underwent nontherapeutic celiotomies were men (61% for metastatic and 59% for locally advanced disease). There was no significant difference for patients who underwent pancreaticoduodenectomy compared with patients who underwent nontherapeutic celiotomies with respect to age. Men were more likely to undergo nontherapeutic celiotomies than women with 61 per cent of the patients undergoing nontherapeutic laparotomy being men, whereas 49 per cent who underwent pancreaticoduodenectomy were men ($P = 0.03$).

Two surgeons undertook 85 per cent of operations. Surgeon volume did not impact the incidence of nontherapeutic celiotomies (Table 1; $P = 0.26$). Seventy-seven (68%) patients had metastatic disease at the time of the operation, whereas 37 (32%) patients had locally advanced unresectable disease. These patients had survivals of 5.0 and 6.0 months, respectively ($P = 0.70$). Survival was not significantly different for patients who underwent nontherapeutic celiotomies for locally advanced or metastatic disease (Fig. 1).

For patients with metastatic disease, 55 (67%) patients had metastatic disease to the liver and 14 (18%) had fine military spread (i.e., carcinomatosis). A total

TABLE 1. *Distribution of Attempted Pancreaticoduodenectomies for Pancreatic Adenocarcinoma Stratified by Surgeon*

Surgeon	Pancreaticoduodenectomies for Pancreatic Adenocarcinoma	Nontherapeutic Operations	Unsuccessful Resections
A	212	68	24%
B	66	29	31%
C	13	7	35%
D	12	1	8%
E	12	1	8%
F	5	3	38%
G	5	3	38%
H	4	2	33%

of 92 metastatic sites were determined intraoperatively for the 77 patients with metastatic disease. A total of 56 sites had locally advanced disease involvement for the 37 patients with locally advanced disease. For patients with locally advanced disease, the portal vein and/or superior mesenteric vein involvement precluding resection occurred in 32 (57%) patients (Tables 2 and 3). One site was found for 64 patients with metastatic disease and 21 patients with locally advanced disease. Up to three sites of metastatic disease were found for two patients and three patients with locally advanced disease.

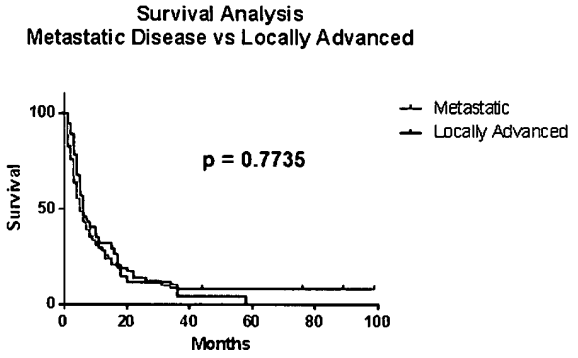

FIG. 1. Survival was not significantly different for patients who underwent nontherapeutic celiotomies for locally advanced or metastatic disease.

TABLE 2. *Metastases and Unresectability by Site for Patients Undergoing a Nontherapeutic Celiotomy for Pancreatic Adenocarcinoma*

Metastasis by Site	n = 92	Locally Unresectable by Site	n = 56
Liver	53	Portal vein	16
Carcinomatosis	14	SMV	16
Mesentery	6	SMA	10
Lymph nodes*	7	Hepatic artery	5
Small bowel	4	Aorta	2
Stomach	1	Small bowel	2
Pelvis	2	Celiac artery	1
Other†	5	Other‡	4

* Lymph nodes: mesenteric, celiac artery, periaortic, periumbilical, superior mesenteric artery (SMV).
† Colon, omentum, unspecified site.
‡ Mesentery, total pancreatectomy required, unspecified site.

TABLE 3. *Site and Distribution of Metastatic Disease*

Metastatic Site	Number of Patients
Liver only	46
Carcinomatosis alone	6
Liver and carcinomatosis	4
Liver and miscellaneous	3
Carcinomatosis and miscellaneous	4
Miscellaneous only	14

Discussion

Patients with pancreatic adenocarcinoma have a generally dismal prognosis.[10] Resection continues to be the only hope of cure with only approximately 20 per cent of patients with pancreatic adenocarcinoma having disease amenable to resection at the time of diagnosis. Despite high-quality preoperative computed tomography (CT) scanning, a portion of patients will undergo intended pancreaticoduodenectomies but will be found to have metastatic disease burden or locally advanced disease that was not recognizable on preoperative imaging. Based on studies with staging laparoscopy, 4 to 36 per cent of patients can potentially avoid a nontherapeutic celiotomy, but staging laparoscopy also misses approximately 5 to 25 per cent of patients who undergo subsequent celiotomy with unresectable disease and adds considerable cost and operative time unnecessary for the vast majority of patients.[7] Staging laparoscopy also increases operative time for patients who underwent subsequent celiotomy and adds the risk of laparoscopic site recurrences (0 to 2%).[7] This study was undertaken to determine nontherapeutic celiotomy incidence, identify risk factors for nontherapeutic celiotomy, and evaluate whether surgeon volume of pancreaticoduodenectomy for pancreatic adenocarcinoma impacted the incidence of nontherapeutic celiotomy for patients undergoing an intended pancreaticoduodenectomy.

This is a retrospective study that shows surgeon volume does not affect the rate of nontherapeutic celiotomy for patients undergoing intended pancreaticoduodenectomy. The surgeons did not use staging laparoscopy before celiotomy. The majority of patients who underwent nontherapeutic celiotomies were the result of imaging-occult metastatic disease with just less than half of the patients having liver metastases too small to be detected on preoperative CT scans. Approximately one-third of the patients who underwent nontherapeutic celiotomies were found to have locally advanced disease that precluded resection. Patients who underwent nontherapeutic celiotomies were more likely to be men.

Although staging laparoscopy and preoperative positron emission tomography (PET) for all patients with pancreatic adenocarcinoma have not been shown to benefit patients,[11-13] a subset of patients with a high likelihood of metastatic disease not found on conventional imaging may still benefit from staging laparoscopy or PET scanning. Patients with a higher propensity for metastatic or locally advanced disease include patients with a very high CA19-9 (100 U/mL or greater),[14]

tumor size on CT 3 cm or greater and weight loss 20 pounds or greater, tumor size on CT 4 cm or greater and weight loss 10 pounds or greater,[15] abdominal or back pain requiring pain medication at the time of presentation,[16, 17] 90° or greater abutment of the portal vein (PV), superior mesenteric vein (SMV), PV/SMV confluence, new-onset ascites or bilateral lower extremity edema, and patients who undergo neoadjuvant chemotherapy for locally advanced disease. To decrease the incidence of nontherapeutic celiotomies, one should use preoperative PET scans for those at very high risk and then staging laparoscopy only when appropriate for small metastatic disease evident on PET scans. This will obviate unnecessary staging laparoscopy.[15]

Patients with pancreatic adenocarcinoma all have a dismal prognosis with the vast majority of patients ultimately dying from progressive disease burden.[18–20] This occurs despite complete tumor extirpation. Therefore, it is reasonable to presume that all patients die from disease burden despite complete tumor extirpation had metastatic disease at the time of the operation that was not conventionally detectable. Given this presumable disease burden beyond the confines for all patients with resectable pancreatic adenocarcinoma, it is important to advocate adjuvant therapy for all patients to undergo resection.

To improve on survival after complete resection, we need to focus on therapies to combat the presumed occult disease at the time of extirpation. Therefore, we are going to undertake a randomized control trial for patients with resectable pancreatic adenocarcinoma; one arm will receive neoadjuvant followed by adjuvant gemcitabine and Abraxane (protein-bound paclitaxel) and the other arm will undergo upfront resection followed by adjuvant gemcitabine and Abraxane. Phase I/II studies have shown a significant additional benefit in adding Abraxane to gemcitabine for patients with pancreatic adenocarcinoma.[21]

Because one-fourth of patients with resectable disease on CT undergo nontherapeutic celiotomies, neoadjuvant therapy will allow for the patients with increased tumor burden to potentially have locally advanced disease regress or continue to develop additional tumor burden that will become evident on standard CT. Therefore, the lead-time bias of imaging-occult metastatic or locally advanced disease will be overcome with a combination of time and treatment with efficacious chemotherapy. Focus on efficacious neoadjuvant/adjuvant therapies as well as thorough preoperative evaluations for patients with a high risk for nontherapeutic celiotomies should be undertaken with every effort to aggressively seek complete tumor extirpation for patients with pancreatic adenocarcinoma. Aggressive resections should continue to be sought, because complete tumor extirpation continues to be the only chance for patients with pancreatic adenocarcinoma to have long-term survival, but the obvious issue with high rates of nontherapeutic celiotomies cannot be ignored.

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