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Laparoscopic vs. Open Resection of Noninvasive Intraductal Pancreatic Mucinous Neoplasms

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Abstract
Required resection margins for noninvasive intraductal papillary mucinous neoplasms (IPMNs) are a controversial issue. Over a 10-year period we have resected IPMNs from the entire pancreatic gland with minimally invasive techniques and compared our survival and complication rates with open controls to see if any difference in resection margins and outcomes could be observed. Data were collected retrospectively, including our first cases of advanced laparoscopic resections. Five-year Kaplan–Meier curves were calculated and statistical analysis was performed using the log rank and Student's *T* test for continuous variables. Chi square and Fisher's exact tests were used for analyzing categorical variables. From March 1997 to Febuary 2006, we operated on 22 patients with noninvasive IPMNs, of which 9 (41%) were operated on laparoscopically and 13 (59%) using open techniques. Three patients underwent laparoscopic duodenopancreatectomy, compared to five in the open group. All resection margins were negative, but two patients required total pancreatectomy, both of which were performed laparoscopically. One of these was converted to open (11%) because of difficulty in reconstructing the biliary anastomosis. The overall complication rates were 56% for the laparoscopic group and 85% for the open group. Twenty-two percent of the laparoscopic group required reoperation and 11% required percutaneous drainage, compared to 15 and 23% in the open group, respectively. All patients are alive after a mean of 20 months (range=2–43) in the laparoscopic group and 37 months (range=1–121) in the open one ($p>0.05$). Laparoscopic resection of noninvasive IPMNs of the entire pancreatic gland has similar complication and survival rates as open procedures. As a result, the laparoscopic approach is appropriate for noninvasive IPMNs of the entire pancreatic gland; however, larger cohorts are needed to see if any approach has superior outcomes. Because of these favorable results, studies are currently underway to see if the minimally invasive approach is also appropriate for invasive IPMNs.

Keywords IPMN · Intraductal · Pancreatic · Mucinous · Neoplasm · Laparoscopic

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) were first recognized over three decades ago and subsequently reported by varying names.[1,2] Recognizing the need for a unifying nomenclature, a classification system for mucinous tumors of the pancreas was described by the World Health Organization in 1996, differentiating IPMNs from other mucinous cystic tumors of the pancreas.[1] Since this time, IPMNs have been reported with greater frequency, but difficulties in differentiating these lesions from mucinous cystic neoplasms (MCNs) have persisted.[3–5] As a result, international consensus guidelines for the management of IPMNs and MCNs were published in 2006 to help physicians properly diagnose and treat these lesions. The current definition of IPMN is an intraductal, mucin-producing neoplasm with tall, columnar, mucin-containing epithelium with or without papillary projections. The pancreatic ducts are extensively involved, and as opposed to MCN, IPMNs lack ovarian-type stroma.[1,3,4] As with mucinous cystadenocarcinomas, invasive IPMNs have been reported to recur after margin negative pancreatic resec-

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tions; however, unlike benign MCNs, noninvasive IPMNs have also been reported to recur after R0 pancreatic resections.[3] The potential multifocality and late recurrence of invasive and noninvasive IPMNs has made surgical management particularly troublesome.

Since Gagner's first reports of pancreatic resections, pancreatic surgeons have concomitantly been making advances in the field of minimally invasive hepato-pancreato-biliary surgery. Currently, conventional indications for pancreatic resections include benign pancreatic tumors that are small and confined to the body and tail of the pancreas. Controversy currently exists as to the need for negative margins in noninvasive IPMNs and the suitability to perform these resections laparoscopically. Because of concerns with adequacy of oncological margins via the minimally invasive approach, we compared our laparoscopic IPMN outcomes and complication rates with our open experience.

Methods

Data were reviewed retrospectively during a 10-year period when IPMNs of the entire pancreas were removed laparoscopically. Survival and complication rates were then compared with open controls. Statistical analysis was performed using Student's *T* test for continuous variables and chi square and Fisher's exact tests were used for analyzing categorical variables (Excel, Microsoft, Redmond, WA, USA).

All patients presenting with symptoms of either jaundice, abdominal pain, or diarrhea were considered for surgery. Preoperative work-up included an echo-endoscopy and cholangiogram via endoscopic retrograde pancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP). Preoperatively, tumors were stratified into main duct, branch duct, or combined variants preoperatively because the rate of malignancy seems very different (15% for lateral ducts, 70% for the main pancreatic duct), despite the absence of clear differences in survival for others.[3] The operative approach for main duct and combined variants was anatomic R0 resection.[6] All pancreatic tumors were approached laparoscopically by one surgeon and by open techniques by two other surgeons. For the minimally invasive surgeon, even tumors with preoperative evidence of invasion of the superior mesenteric or portal vein were approached laparoscopically and only converted to open for the vascular reconstruction. Preoperative evidence of invasion of the superior mesenteric artery or metastases were considered contraindications for surgery, and neo-adjuvant chemotherapy was considered.

In high-risk patients with a branch duct variant, enucleation with negative frozen section of the efferent duct was attempted for tumors in the head and neck of the pancreas.[7] Noninvasive IPMNs were stratified into adenoma, borderline neoplasms, and carcinoma in situ (CIS) on histopathology. Invasion was diagnosed when patients were found to have documented histopathological evidence of tumor cells infiltrating the pancreatic connective tissue or metastasis. All patients underwent intraoperative frozen section analysis to confirm presence of negative margins. Total pancreatectomy was performed when negative margins could not be accomplished after re-resection for both invasive and noninvasive tumors, although recent evidence suggests that this may not be necessary for noninvasive tumors.[8]

Complications were defined as major and minor according to the classification system devised by Dindo et al.[9] Any complications that could be managed with medication and fall into category grade IIIa or less were considered minor complications. Any complication that required an intervention, percutaneous or surgical, was considered a major complication; this corresponds to a grade IIIb complication or higher.[9] Five-year actuarial survival was calculated according to Kaplan–Meier, any difference was analyzed with the log rank test to ascertain statistical significance (Excel, Microsoft).

Results

From March 1997 to Febuary 2006 we operated on 36 patients for IPMN's, of which 9 (25%) were operated on laparoscopically and 27 (75%) using open techniques. A total of 14 patients were found to have invasive disease on final pathology. All of these cases were approached via open techniques. Of the remaining patients, 9 (41%) were operated on laparoscopically and 13 (59%) with open techniques (Table 1). The first laparoscopic procedure was performed in 2001. The average age for the laparoscopic group was 58 years compared to 63 in the open group. The

Table 1 Patient Statistics of 22 Patients Undergoing Pancreatic Resection for Noninvasive IPMN, Laparoscopic vs. Open

	Laparoscopic	Open
Number	9	13
Age (years)	58	63
Tumor size (cm)	3.0	3.1
Operative time (min)	274	339
Blood loss (mL)	143	281
LOS (days)	20	24
Average follow-up (months)	20	37

Overall morbidity includes the total number of major and minor complications (see Table 4); none of the differences were statistically significant ($p>0.05$)

mean tumor sizes were also similar at 30 mm and 31 mm for the laparoscopic and open groups, respectively. The mean operative times and estimated blood loss were 274 min and 143 mL, compared to 339 min and 281 mL.

The distribution of procedures is seen in Table 2. Duodenopancreatectomy (DPC) was performed laparoscopically in three patients and in five patients via laparotomy. Distal pancreatectomy with splenic preservation was performed in two and three patients in the laparoscopic and open groups, respectively. Central pancreatectomy was performed in one patient via laparotomy. Total pancreatectomy was performed laparoscopically in two patients. One patient had a previous distal pancreatectomy for a noninvasive CIS IPMN at another institution, and the resultant open DPC was essentially a completion of a total pancreatectomy. Enucleations in the head of the pancreas were performed in the remaining patients, two in the laparoscopic group and two in the open group. An additional two patients underwent open extended enucleations or limited resections in the uncinate process and neck, respectively. In the invasive cohort, eight patients necessitated a DPC, five a distal pancreatectomy, and one a total pancreatectomy. All resection margins were negative, but, as mentioned, a total of four patients required total or completion pancreatectomy. Distribution of subclassifications of noninvasive tumors into adenoma, borderline, and CIS is shown in Table 3. Among the patients with noninvasive disease, an average of 13 lymph nodes (range=10–24) were retrieved after laparoscopic DPC, compared to an average of 16 (range=14–26) in the open group.

One laparoscopic procedure was converted to open (11%) because of difficulty in reconstructing the biliary anastomosis after total pancreatectomy. Five patients (56%) operated on laparoscopically suffered complications (Table 4), two of which required interventions (22%). The first was due to postoperative hemorrhage from a pseudoaneurysm of the gastroduodenal artery (GDA), which was embolized by interventional radiology. The other patient suffered an upper gastrointestinal bleed from the pancreaticogastrostomy, which had to be taken down and redone. Other complications in the minimally invasive group included pancreatic fistula in a total of three patients, requiring drainage in one (11%) patient. One of these cases occurred in the patient with the postoperative bleed from the GDA; fortunately, this complication did not require reoperation.

Among the open cases, 11 patients with noninvasive disease (68%) suffered either major or minor complications (Table 4). A total of five patients suffered major complications, two (15%) of which required reoperation. One patient developed a gastric volvulus postoperatively that was also further complicated by an acute attack of pancreatitis. One patient bled postoperatively from the right hepatic artery and required urgent surgery. This patient subsequently developed a pancreatic fistula that did not require surgery. Three other patients (23%) required drainage of abscesses, two of which were associated with pancreatic fistulas. The remaining minor complications included intra-abdominal

Table 2 Distribution of Procedures Done for Noninvasive Intraductal Papillary Neoplasms, Laparoscopic vs. Open

	Laparoscopic	Open
Total	9	13
DPC	3	5[a]
Splenic-preserving left pancreatectomy	2	3
Total pancreatectomy (conversion)	2 (1)[b]	0
Enucleation (pancreatic wedge resection)	2	2 (2)
Central pancreatectomy	0	1

[a] DPC after left pancreatectomy resulting in completion total pancreatectomy

[b] After the resection, this patient had to be converted to open to perform the bili-enteric anastomosis

Table 3 Final Histopathology of all Noninvasive Intraductal Papillary Neoplasms

	Laparoscopic	Open
Adenoma	3	4
Borderline	4	6
CIS	2	3

Table 4 List of Overall Complications in Patients with Noninvasive Intraductal Papillary Neoplasms

	Laparoscopic	Intervention Required (%)	Open	Intervention Required (%)
Total patients	5 (56)	3 (33)	11 (85)	5 (38)
Pancreatic fistula	3	1 (11)	3	2 (15)
Postoperative hemorrhage	1	1 (11)	1	1 (8)
Intra-abdominal abscess	0	0	3	1 (8)
Necrotizing pancreatitis	0	0	1	0
Upper gastrointestinal bleed	1	1 (11)	0	0
Urinary tract infection	0	0	1	0
Gastric volvulus	0	0	1	1 (8)
Biliary fistula	0	0	1	0
Wound infection	0	0	1	0

Intervention consisted of surgery or percutaneous drainage performed by interventional radiology

fluid collections, biliary fistula, and urinary tract and wound infections.

In the invasive group, 53% of patients suffered complications. One patient presented with necrosis of the right hepatic artery that required a vein graft and was complicated by necrotizing pancreatitis necessitating multiple repeat trips to the operating room. This patient left the hospital after almost 11 months of a prolonged stay in the intensive care unit. Other complications in the invasive group included two partial splenic infarctions that did not require surgery and were treated with antibiotic prophylaxis.

There were no perioperative mortalities. In the noninvasive cohort, the average hospital stay and follow-up was 20 days and 20 months (range=2–43) in the laparoscopic group and 24 days and 37 months (range=1–121) in the open group; none of these differences was statistically significant. As opposed to institutions in North America, patients are usually kept in the hospital until all drains are removed even if they may be ambulating and tolerating a regular diet. In the invasive group, the average length of stay (LOS) was 46 days (range=4–311) and the mean follow-up was 34 months. The overall survival rates were 100% for the laparoscopic and open noninvasive groups and 51% for the group with invasive disease.

Discussion

In an effort to guide the practicing surgeon, a complex system of histopathological classification of IPMNs has been developed and studied. Initial studies differentiated IPMNs that are isolated to the main pancreatic duct from lesions in the smaller ducts, so-called branch duct variant.[10] Combined variants contain components of both types. Although many authors have attempted to ascertain differences in outcomes among these groups, the largest single center experience with IPMNs noted no statistically significant differences in survival, although they did find that the branch–duct variant is more commonly noninvasive.[3] Nonetheless, multiple centers have noted that main duct and combined variants are more often invasive.[11,12] Studies from Japan have found that main duct types and/or the presence of mural nodules are predictive of malignancy and invasion.[12,13]

Although pathologists have further classified noninvasive IPMNs into adenomas, borderline neoplasms, and CIS, the Johns Hopkins group noted no differences in survival. Invasive groups have been further classified into tubular, colloid, mixed, and anaplastic types by some groups.[3] Interestingly, the Hopkins group did find a survival advantage in patients with colloid carcinomas as compared to tubular carcinomas.[3] A new consensus conference in 2005 created an IPMN classification system that separates IPMNs into gastric, intestinal, pancreatobiliary, and oncocytic subtypes.[2] According to Asian studies, branch duct variants are more often gastric-type (98%), and main duct variants are more often intestinal-type (73%); furthermore, 23% of intestinal type IPMNs are found to be invasive vs. 2% for the gastric-type.[14] Because of the current controversy involving classifications of IPMNs, our department of pathology does not subclassify invasive IPMNs.[14]

Prior to the consensus conference of 2006, our operative approach was to resect all noninvasive and invasive IPMNs until an R0 resection could be achieved.[15] This was done by intraoperative frozen section analysis.[16] Unfortunately, this resulted in two patients with noninvasive IPMNs undergoing total pancreatectomy and having to live a life with the difficult task of managing brittle diabetes with all of its associated sequelae, which can even include death.[6] According to the new guidelines, adenomas that are not symptomatic can be observed with yearly screening. Borderline noninvasive cases are still debatable, but it was the consensus that all CIS patients regardless of presence or absence of symptoms should undergo surgery.[15] This argument was extended to include all noninvasive subtypes because of the low risk of tumor recurrence in microscopically positive resection margins.[17] Invasive tumors have a similar natural history to pancreatic adenocarcinomas and R0 resections are the standard of care.[18–20]

At our institution, we attempt preoperative localization in all patients with a suspected IPMN to aid the operative approach, specifically, port placement and patient positioning. The pancreatic duct is imaged via ERCP or MRCP; however, many patients are often diagnosed after helical CT with very thin slices, intravenous contrast, and a pancreatic protocol including a rapid arterial phase.[21] All patients also undergo endoscopic ultrasound to determine whether or not the main pancreatic duct is involved and the proximity to the superior mesenteric vessels and portal veins.[22] In difficult cases we also obtain endoscopic ultrasound fine needle aspirations to assist in our preoperative diagnosis.[23,24] Smaller tumors without evidence of obvious invasion are classified as pancreatic intraepithelial neoplasia and observed.[3,25] Because of the increased risk of malignancy in main duct IPMNs, formal resection is recommended, although recent work suggests that asymptomatic branch duct IPMNs can be observed.[10,25,26] Patients who are good operative candidates, with main duct disease, are offered surgery. High-risk patients with small tumors (<10 mm) can be observed, but all patients regardless of operative risk are offered surgery if they have preoperative evidence of intramural nodules because of increasing evidence that these tumors have a high risk of invasiveness.[27]

Prior to this study, the GDA was clipped laparoscopically with plastic locking clips and reinforced with a 4.0

nonabsorbable suture ligature. Currently, we employ only titanium clips with silk suture ligature or use the endoscopic vascular TA stapler. We now only preserve the spleen when the splenic vein can be preserved without any evidence of tear or stenosis. Ideally, the splenic artery and vein are spared in localized tumors (malignant or benign) of the distal pancreas necessitating resection of the tail; however, if necessary, the splenic artery can be sacrificed proximally if the arterial blood supply via the gastroepiploic is left intact. The splenic vein is always preserved because of reports of delayed segmental portal hypertension after transection of this structure in cases of splenic preservation.[28] If this is not possible, a splenopancreatectomy should be considered.

Limitations of this study are the small number of the cohorts, the fact that only one surgeon performed procedures laparoscopically, and the fact that both cohorts were not completely concomitant. Specifically, the first laparoscopic procedure was done 4 years after the first open IPMN resection. Comparisons with other international institutions are also difficult due to the fact that we have no incentive to discharge patients early, which may partially explain why our LOS may be longer than other results reported in the literature. Nonetheless, the fact that no significant differences exist in LOS when our two groups are compared indicates that this does not seem to be significantly effected. Another problem with our study is the high rates of reoperation and need for percutaneous drainage. This fact, however, is tempered by the fact that we have no perioperative mortalities, which is notably lower than that normally reported in the literature.

Conclusions

The minimally invasive management of IPMNs has been hindered by the fact that many of these tumors present in the head of the pancreas. Surgeons have been reluctant to embrace laparoscopic techniques for lesions in the head of the pancreas because of the perceived difficulty in dissecting the head of the pancreas off of the portal vein, superior mesenteric vein, and superior mesenteric artery and the complexity of the reconstruction. Nonetheless, as more and more surgeons gain experience in both hepato-pancreato-biliary surgery and minimally invasive techniques, the indications for minimally invasive approaches to pancreatic pathology have been increasing.

At our institution, we have now successfully performed eight out of nine laparoscopic procedures for the treatment of noninvasive IPMN. These tumors have identical overall 5-year survival rates to open controls. Overall major and minor complication rates and reoperation rates are similar. Although this series is small, it would appear, in high-volume centers with experience in both pancreatic and laparoscopic surgery, that the minimally invasive approach is appropriate for the management of noninvasive and invasive IPMNs of the entire pancreatic gland; however, larger cohorts are needed to see if any approach has superior outcomes. Because of these favorable results, studies are currently underway to see if the minimally invasive approach is also appropriate for invasive IPMNs.

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