Impact of Laparoscopic Staging in the Treatment of Pancreatic Cancer

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Hypothesis: Staging laparoscopy in patients with pancreatic cancer identifies unsuspected metastases, allows treatment selection, and helps predict survival.

Design: Inception cohort.

Setting: Tertiary referral center.

Patients: A total of 125 consecutive patients with radiographic stage II to III pancreatic ductal adenocarcinoma who underwent staging laparoscopy with peritoneal cytologic examination between July 1994 and November 1998. Seventy-eight proximal tumors and 47 distal tumors were localized.

Interventions: Based on the findings of spiral computed tomography (CT) and laparoscopy, patients were stratified into 3 groups. Group 1 patients had unsuspected metastases found at laparoscopy and were palliated without further operation. Group 2 patients had no demonstrable metastases, but CT indicated unresectability due to vessel invasion. This group underwent external beam radiation with fluorouracil chemotherapy followed in selected cases by intraoperative radiation. Patients in group 3 had no metastases or definitive vessel invasion and were resection candidates.

Main Outcome Measure: Survival.

Results: Staging laparoscopy revealed unsuspected metastases in 39 patients (31.2%), with 9 having positive cytologic test results as the only evidence of metastatic disease (group 1). Fifty-five patients (44.0%) had localized but unresectable carcinoma (group 2), of whom 2 (3.6%) did not tolerate treatment, 20 (36.4%) developed metastatic disease during treatment, and 21 (38.2%) received intraoperative radiation. Of 31 patients with potentially resectable tumors (group 3), resection for cure was performed in 23 (resectability rate, 74.2%). Median survival was 7.5 months for patients with metastatic disease, 10.5 months for those receiving chemoradiation, and 14.5 months for those who underwent tumor resection (P < 0.01 for group 2 vs group 1; P < .001 for group 3 vs group 1).

Conclusions: Staging laparoscopy, combined with spiral CT, allowed stratification of patients into 3 treatment groups that correlated with treatment opportunity and subsequent survival. Among the 125 patients, laparoscopy obviated 39 unnecessary operations and irradiation in patients with metastatic disease not detectable by CT. Laparoscopic staging can help focus aggressive treatment on patients with pancreatic cancer who might benefit.

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The main goal of staging protocols for pancreatic cancer is to categorize patients into groups to optimize strategic decisions and response to treatment. Three groups are frequently recognized. The first group includes individuals who present with metastatic disease. Surgery is best avoided in these patients in view of their short survival time, and chemotherapy is their principal treatment modality. The second group comprises patients with advanced local disease (ie, major vascular invasion) but without metastases. These patients can benefit from external beam radiotherapy (EBRT) combined with chemotherapy and, according to their response, are candidates for intraoperative radiation (IORT). A third and last subpopulation is patients with resectable tumors. These individuals may benefit from transfer to a tertiary referral center where pancreatic resection can be performed with low mortality rates. They may also be candidates for protocols that combine surgery and IORT or local hepatic chemotherapy and aim to improve current surgical results.

The most powerful noninvasive diagnostic test for evaluation of suspected pancreatic cancer is high-resolution, contrast-enhanced spiral computed tomography (CT). Computed tomography is
PATIENTS AND METHODS

A total of 125 consecutive patients with radiographic stage II to III pancreatic ductal adenocarcinoma underwent staging laparoscopy at our institution between July 1994 and November 1998. Histologic confirmation of diagnosis was ultimately obtained in all cases. Patients with radiologic stage I pancreatic cancer (tumors < 2 cm) are not included, since we do not perform laparoscopy in these cases given the low yield of unsuspected metastases. Patients with bile duct, ampullary, duodenal, and pancreatic endocrine or acinar tumors were excluded from the study population, as were patients with cystadenocarcinoma or intraductal papillary mucinous tumors. In addition, patients with gastric outlet obstruction were excluded, because laparotomy was indicated regardless of the findings at laparoscopy. All patients underwent thin-section, contrast-enhanced spiral CT preoperatively to evaluate the primary tumor and adjacent structures, rule out metastatic disease, and evaluate large vessel invasion (portal vein, superior mesenteric vessels, and celiac axis). Angiography was used in a small minority of patients (n = 21) in whom CT findings were questionable. All patients without metastatic disease, irrespective of vessel invasion, were considered candidates for laparoscopy.

Based on the combined findings of CT and laparoscopy, patients were divided into 3 groups according to the management algorithm illustrated in Figure 1. Patients in group 1 were found to have unsuspected metastases at laparoscopy and were offered chemotherapy, some opting for no treatment. Group 2 patients, who had no metastases detected at laparoscopy but had obvious vessel encasement apparent on CT, underwent EBRT with fluorouracil chemotherapy. Selected patients who completed this regimen without interval development of metastatic disease received a booster dose of IORT. Finally, patients in group 3 had no metastatic disease at laparoscopy and only vessel encroachment but not encasement apparent on CT. These patients were considered candidates for resection.

Patient survival from the date of staging laparoscopy was assessed during February and March 1999 and this information was available for 93% of patients. Survival data were obtained through telephone interviews with patients or family members, physicians’ and surgeons’ office notes, or the hospital cancer registry. Data obtained are presented as Kaplan-Meier survival curves.

Statistical analysis involved the Fisher exact test and Wilcoxon rank sum test (for Kaplan-Meier plots). $P<.05$ was accepted as significant.

The main purpose of laparoscopy is to identify metastatic dissemination not detectable by CT. Patients undergo examination under general anesthesia as outpatients or with a 23-hour observation stay. Following establishment of pneumoperitoneum, a 10-mm trocar is inserted through a small infraumbilical incision. The telescope is introduced through this trocar, and examination begins by inspection of the lower abdomen and pelvis. The lower abdomen is a frequent site of peritoneal metastasis in pancreatic cancer, and laparoscopic visualization of this area is often superior to laparotomy. Free fluid is aspirated and saved for cytologic examination. The laparoscope is then rotated for examination of the upper quadrants. Inspection begins by assessment of the omentum and the subdiaphragmatic spaces. Meticulous examination of the liver surface is essential. Insertion of a second 5-mm trocar in the right upper quadrant is necessary for adequate evaluation of the undersurface of the liver. A rod inserted through this second trocar site is used to elevate the liver, allowing inspection of the gallbladder fossa and liver hilum. We do not perform extensive dissection of the retrogastric space or use laparoscopic ultrasound.

Peritoneal washings are performed before further dissection or biopsy to prevent sample contamination. Subsequently, biopsies are performed on all suspicious peritoneal or omental nodules using forceps inserted through the second trocar site. Access to lesions in the pelvic peritoneum may require insertion of a third 5-mm trocar in the lower midline. Biopsies on implants in the liver are most easily performed using the Tru-Cut needle (Travenol Laboratories, Deerfield, Ill) inserted directly through the abdominal wall or by biopsy forceps through the second trocar site. The entire procedure takes 20 to 30 minutes.

PATIENT POPULATION

Characteristics of the patient population are summarized in Table 1. Sixty-two percent of patients had tumors localized to the head of the pancreas, of whom 65% presented with jaundice. Average tumor size was greater than 3 cm, consistent with locally advanced disease (stage II-III). Neoplasms in the distal pancreas were larger on average than those in the head of the gland. Vascular encasement by CT criteria was noted in 66% of patients.
STAGING LAPAROSCOPY

Table 2 illustrates the frequency of unsuspected metastatic disease found during staging laparoscopy. Thirty-one percent of patients had unsuspected metastatic disease not detected by CT, and in 23% of these patients (9 patients, 7.2% of total group) metastases were evident only by peritoneal cytologic examination. Gross metastases and positive cytologic test results were more frequent in tumors of the body or tail of the pancreas, consistent with the more advanced growth of these tumors. Micrometastases, indicated by positive peritoneal cytologic test results, were detected frequently (52.2%) in tumors that demonstrated gross intraperitoneal spread, but micrometastases without visible macrometastatic accompaniment occurred in 42.9%.

Only one postoperative complication occurred in 125 staging laparoscopies (complication rate, 0.8%). This was an umbilical trocar site abscess that required surgical drainage. The sensitivity of the staging procedure was calculated by evaluating the laparotomy findings in 31 patients explored shortly after laparoscopy (group 3). A single patient had a liver metastasis missed at laparoscopy, yielding a sensitivity of 97%. The specificity of the test was judged to be 100%, since all patients with positive results had cancer demonstrated on biopsy samples.

TREATMENT GROUPS

Thirty-nine patients (31.2%) were found to have metastatic disease at laparoscopy (group 1). Patients without metastases at laparoscopy included 55 (44.0%) with definite vessel encasement apparent on CT (group 2) and 31 (24.8%) without vessel invasion apparent on CT (group 3).

Of the 55 patients in group 2, two (3.6%) did not tolerate EBRT with fluorouracil chemotherapy because of severe adverse effects, and 20 (36.4%) developed metastatic disease during this treatment, eliminating their candidacy for IORT. Twenty-seven patients (49.1%) fulfilled criteria for IORT, and 21 (38.2%) consented and received such treatment.

All patients in group 3 underwent exploratory laparotomy shortly after staging laparoscopy. The tumors of 23 patients were resected for cure, yielding a resectability rate of 74.2% for the 31 patients explored with intention to resect their tumors. Operations performed included 19 pancreaticoduodenectomies, 3 distal pancreatectomies with splenectomy, and 1 total pancreatectomy. As mentioned previously, 1 patient was found to have an unsuspected liver metastasis at laparotomy. The remaining 7 patients, whose tumors were found to be unresectable because of vessel encasement that was underappreciated by CT assessment, underwent palliative biliary and duodenal bypass procedures.

SURVIVAL

Survival data were obtained for all patients (Figure 2). Median survival was 7.5 months for patients in group 1, 9 months for patients in group 2, and 13 months for those in group 3 ($P = .14$ for group 1 vs group 2; $P < .001$ for group 1 or 2 vs group 3). Patients with localized unresectable disease (group 2) were further subdivided into those who developed metastatic disease during EBRT and fluorouracil chemotherapy ($n = 20$) and those who completed treatment without interval development of metastases and received IORT ($n = 21$). Survival for these 2 subgroups is illustrated in Figure 3, which shows that survival for patients stratified to group 2 who developed metastatic disease during treatment was identical to that in group 1.
Appropriate treatment of patients with pancreatic cancer depends on accurate staging of their disease. Although complete resection offers the only chance for cure, surgical exploration of most of these patients is no longer necessary to establish unresectability. Patients with metastatic disease can benefit from minimally invasive percutaneous and endoscopic techniques, which allow tissue sampling and treatment of malignant biliary obstruction\textsuperscript{16,17} without the potential morbidity and convalescence time characteristic of surgical approaches\textsuperscript{18}. Ninety-seven percent of patients treated with only minimally invasive techniques never require a laparotomy\textsuperscript{19,20}.

Our results demonstrate that 31% of patients with negative CT examination results were found to have occult metastatic disease at laparoscopy. Therefore, staging laparoscopy prevented 39 unnecessary surgical explorations, and more than 95% of these patients have not required further surgery. Staging laparoscopy was efficient in the detection of metastases, showing a sensitivity of 97%. These findings mirror those of a previous cohort from our institution\textsuperscript{13}. Metastatic implants or positive peritoneal cytologic test results were more frequent in tumors of the distal pancreas than those in the proximal gland, which is consistent with their usual lack of significant symptoms and more advanced stage at presentation.

We use peritoneal cytologic testing to detect very early, invisible metastatic disease. The combination of peritoneal cytologic testing and simple laparoscopy has increased our detection of occult metastases from 24% to 31%, with 9 patients having positive cytologic test results as their only evidence of metastases. Several studies\textsuperscript{21-25} have evaluated the significance of positive peritoneal cytologic test results (micrometastases) in the absence of gross metastases in patients with pancreatic cancer. Most studies confirm that positive cytologic test results are an indicator of unresectable, aggressive disease characterized by early metastasis and short survival times. In fact, no difference in survival times exists between patients with gross metastasis detected at laparoscopy and those with positive cytologic test results but no visible metastatic disease\textsuperscript{22}. We have advocated classification of patients with positive peritoneal cytologic test results as M1 in the TNM system\textsuperscript{22}, as is the case for gastric\textsuperscript{26}, ovarian\textsuperscript{27}, and endometrial\textsuperscript{28} cancers. These patients do not derive further benefit from surgical resection or radiation therapy.

The main goal of staging laparoscopy in patients with pancreatic cancer is the identification of unresectability...
due to metastasis or portal vein invasion (if laparoscopic ultrasound is added\cite{11,12,14}). Many centers have evaluated the success of their staging protocols by the resectability rates following diagnostic laparoscopy,\cite{11,12,14} but the focus should properly be on identifying those who have cancer beyond reasonable bound of removal.\cite{29} “Resectability” depends in part on the surgeon’s willingness to resect and reconstruct major vascular structures\cite{30} or leave tumor behind (“palliative resection”)\cite{31} and may not reflect the accuracy of the staging protocol.

We use staging laparoscopy not only to select patients with resectable disease but also to evaluate those with localized unresectable disease due to major vessel encasement who can benefit from local radiation therapy. Current trends for aggressive multimodality treatment of locally advanced carcinomas (combinations of radiotherapy and chemotherapy) underscore the importance of excluding metastatic disease.\cite{32} The morbidity, cost, and time commitment required by these new treatment modalities are not negligible, and patient selection is as important as for surgical resection. Other centers that offer similar neoadjuvant therapies also include laparoscopy in their staging protocols.\cite{21}

Our study demonstrates that staging laparoscopy and abdominal CT allow stratification of patients into 3 treatment groups based on the presence or absence of occult metastases and vascular invasion. Previously, our staging algorithm required angiography to evaluate the status of vascular structures adjacent to the primary tumor mass.\cite{13} During the past 4 years, improvements in the CT resolution of vascular structures have rendered angiography obsolete in most cases.\cite{8} A comparison between a previous series from our institution\cite{14} with the present series reveals almost identical resectability rates (75% and 74%, respectively) despite our current disuse of routine angiography.

One of the main goals of this study was to investigate if subdivision of patients by our staging protocol correlated with prognosis. The data confirm shortest and longest survival for patients with metastatic and resectable neoplasms, respectively, with intermediate survivals occurring in those with localized but unresectable disease. It appears that patients in group 2 may be further subdivided into those who progress rapidly to demonstrable metastatic disease vs those who remain localized during EBRT, having shorter and longer survivals, respectively. Differentiation between these 2 patient subgroups remains a challenge that may only be met with new genetic markers or behavioral indices for cancer. Other differences in survival among our groups and subgroups may reflect timing of disease detection (early vs late), individual tumor biology, treatment efficacy, or a combination of factors.

Recent published series\cite{11,12,14} have demonstrated that laparoscopic ultrasound or extended laparoscopic dissection can further enhance the accuracy of the staging procedure. These studies have demonstrated resectability rates close to 90% and have used this information to support extensive and exhaustive staging procedures. However, in our experience the added value of laparoscopic ultrasound to the vascular staging provided by a good spiral CT with vascular enhancement is minimal, and laparoscopic dissection of the portal-mesenteric vein is time-consuming, potentially dangerous, and beyond the skills of the nonexpert. In our view, staging laparoscopy should be a tool both for the high-volume pancreatic surgeon and for the general surgeon to identify patients who can be well palliated in the community setting and those who may benefit from transfer to specialized centers for aggressive therapy.

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William Meyers, MD, Worcester, Mass: This is the latest in a long list of studies from a great surgical group that has consistently blessed the surgical literature. The studies represent an accumulation of an immense amount of data, which lead us into future directions with respect to care of patients with pancreatic cancer. The modern era of laparoscopy has had profound impact on what we surgeons do today. Laparoscopic staging prior to definitive pancreatic or hepatic resection has emerged as a meaningful technique. It is important to pause and reflect on what the present study is telling us and what it is not telling us today. I share with the authors certain biases. Laparoscopy prevents bigger incisions. We should strive to stage patients into groups and be aggressive, particularly with locally unresectable disease. We have made tremendous progress with resection of selected cancers, and neoadjuvant and adjuvant therapy will ultimately have great roles. I do have one practical question that comes up all the time in our practices. When one performs laparoscopy at the same sitting as potential resection, and then one does open the patient and resects, it is very difficult to get the most expensive part of the case, the laparoscopy, paid by the insurance companies. They, the insurance companies, call the operation a “conversion” rather than a staging laparoscopy, and most companies deny payment for the professional or hospital charges related to the laparoscopy and the “conversion.” When one calculates the cost of the lack of payment, this very beneficial technique becomes a financial burden for the hospital and clinical system. How do you address this practical question at your institution? Despite these criticisms, your experience illustrates some promising strides forward in the care of patients with pancreatic cancer. It represents a great experience: the utility of laparoscopy even without ultrasonography, the ability to stage patients, and the importance of staying current with new techniques.

John C. Russell, MD, New Britain, Conn: Two questions. First, you stated that 9 of 91 patients had positive cytology only, which is about 10%. But did you compare pancreatic head lesions with lesions of the body and tail? You found that laparoscopy had a higher yield of grossly metastatic disease (CT scan negative) for body and tail lesions than for tumor of the pancreatic head, but was there a similar difference in cytology-only positive tumors between body and tail tumors vs pancreatic head tumors? If the yield of cytology-positive only pancreatic lesions is below 10%, the added expense of staged preoperative laparoscopy (rather than immediate preoperative laparoscopy) for pancreatic head lesions would not seem justified.

Second, did you study whether any noninvasive modalities, such as serum CA19-9 [cancer antigen 19-9] levels, would predict whether patients who were negative by CT scan would be positive on laparoscopy for either grossly metastatic disease or positive cytology?

Dr Jimenez: I would like to start with Dr Meyers’ questions. The patient survival data presented in our study are dependent on a variety of factors, including tumor biology, timing of the disease detection, treatment administered, and individual response to treatment. Patient survivals are presented as a simple observation, and at no point do we suggest that these survivals are a result of treatments administered. The purpose of presenting the survival data was to illustrate that laparoscopic staging of pancreatic cancer patients correlates with disease survival. We demonstrate that an apparently homogeneous cohort of patients can be subdivided into 3 different groups and that this subdivision helps in allocating treatment and determining prognosis. Ideally, we would have liked to present staging scheme preserves that we are talking about the natural course of the disease and that the treatment regimens were basically similar. These presumptions are easy to support, since one is dealing with such a dismal disease, particularly after the patients with the best prognoses are excluded. It is a mistake for this study to also imply that the authors can select out patients who might benefit from certain therapy. There are just too many variables. Therefore, any implication that survival might be related to a specific therapy in this study or, for example, intraoperative radiation or even resection, is not justified from these data. These are biases and not conclusions. There are certain other parts of the paper that are also a bit misleading, for example, that laparoscopic ultrasound is not useful. The data presented do not address ultrasound, and therefore this conclusion is not appropriate. Many people have different biases plus data about ultrasound, such as Garden and Callery. Likewise, the importance of peritoneal washings and staging seems minimally useful unless this information is obtainable at surgery.
the natural history of our 3 groups of patients by showing their survivals without treatment interventions. However, because the study was a retrospective review, this information was not available.

As Dr. Meyers has mentioned, some centers include laparoscopic ultrasonography in their staging procedures. In particular, there is a recent series (Minnard et al. Laparoscopic ultrasound enhances standard laparoscopy in the staging of pancreatic cancer. Ann Surg. 1998;228:182-187) from Memorial Sloan-Kettering where laparoscopic ultrasound was used to evaluate the liver parenchyma for metastases and to evaluate vessel invasion. These surgeons also perform extensive laparoscopic dissection to examine the porta hepatitis, lesser sac, and celiac axis. Their excellent results show that the combination of laparoscopic dissection and ultrasound allows correct determination of resectability in greater than 95% of patients. We have used laparoscopic ultrasound sparingly and do not use it routinely in our staging laparoscopies. We believe that laparoscopic dissection and ultrasound can significantly lengthen the staging procedure, and we do not recommend laparoscopic dissection near large vessels because of potential bleeding complications. We propose that staging laparoscopy should be a very simple procedure, involving only peritoneal cytology and biopsy of suspicious lesions. Our procedures are usually completed in 20 to 30 minutes.

I am not well qualified to answer questions on procedure reimbursement but can discuss related issues. Our staging laparoscopies are always scheduled as single procedures, and most patients are discharged home on the same day. Patients who require exploration for resection have this done after several days, and therefore none of our laparoscopies qualify as “converted” procedures. The delay between laparoscopy and open exploration allows time to obtain the results of the peritoneal cytology samples.

The second discussant inquired about the results of peritoneal cytology in patients with proximal vs distal tumors of the pancreas. I have shown that tumors of the distal pancreas showed gross metastatic disease almost twice as often as tumors of the head of the gland. Likewise, we found that 36% of distal tumors had positive peritoneal cytology but only 9% of proximal tumors had positive cytology. These findings are consistent with the more advanced stage of tumors of the tail of the pancreas, resulting from their lack of significant symptomatology.

In terms of other tumor markers, such as carcinoembryonic antigen and CA19-9, we frequently use these tests in our preoperative patient evaluations. However, we have not collected these data as part of this study.

Finally, Dr. Dibbins asked about the role of staging laparoscopy in patients with demonstrable vessel invasion on CT. Clearly, these patients are not candidates for resection. The reason they undergo staging laparoscopy is to determine their candidacy for radiotherapy. Radiotherapy is only of benefit to patients with localized disease, and patients with metastatic disease detected by laparoscopy are not offered such treatment.