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REVIEW

Value of Laparoscopy in the Staging of Pancreatic Cancer

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Summary

Pancreatic cancer is a devastating disease that swiftly robs patients of both quality and quantity of life. It is the fourth leading cause of cancer death in the United States. In 2003, there were 31,860 reported new cases with 31,270 deaths occurring due to lack of effective therapy. Eighty percent of patients present with either advanced local or metastatic disease. Dynamic contrast-enhanced computed tomography (CT) has become the current staging test of choice. Laparoscopic staging of pancreatic tumors with the addition of ultrasound can reveal intraparenchymal hepatic metastases, small peritoneal metastases, and critical retro-peritoneal tumor-vessel relationships approaching the accuracy of open exploration to determine resectability without significantly increasing morbidity or mortality. However, given the current accuracy of high-quality CT, the routine use of diagnostic laparoscopy in pancreatic cancer is not warranted. Diagnostic laparoscopy is recommended in select patients with primary tumors greater than 4 cm, tumors in the body or tail of the pancreas, patients with equivocal findings of metastasis on CT, ascites, or clinical or laboratory findings suggesting advanced disease such as marked weight loss, hypoalbuminemia, and elevated CA 19-9.

Introduction

Pancreatic cancer is a devastating disease that swiftly robs patients of both quality and quantity of life. It is the fourth leading cause of cancer death in the United States. In 2003, there were 31,860 reported new cases with 31,270 deaths occurring due to lack of effective therapy [1]. At least 80% of patients with pancreatic cancer present with either locally advanced or metastatic disease and are unresectable at the time of diagnosis. Pancreatic cancer tends to recur after surgery and is relatively resistant to adjuvant therapy thus contributing to a poor overall survival [2]. The overall 5-year survival after resection is somewhere between 15-20%. In patients that fall into the better prognostic groups (such as small tumors, negative lymph nodes, favorable molecular genetics) the 5-year survival can approach 40-50%. However, surgery is currently the only treatment available that offers a meaningful improvement in survival. Therefore, it is critical that we identify patients who might benefit from resection, and avoid a surgical approach in unresectable patients who will be better served with palliative treatment.

Despite recent advances in imaging and non-operative techniques to relieve biliary obstruction, many patients still undergo an exploratory laparotomy for accurate staging and palliation [3, 4, 5, 6, 7]. A negative laparotomy is associated with significant perioperative morbidity and diminishes quality of life postoperatively [6, 8]. Many older studies demonstrate that laparoscopic staging is superior to radiological staging especially with detection of small peritoneal and hepatic disease [9, 10, 11]. With recent advances in minimally invasive surgery, a thorough surgical staging procedure for pancreatic cancer is now possible.

In this review, we identify the limitations of current staging modalities used in pancreatic adenocarcinoma and evaluate the advantages and disadvantages of routine laparoscopy as a staging tool as well as for palliative treatment.

Computerized Tomography (CT)

CT scan has undergone a revolutionary evolution over the last 20 years with new developments that have improved data acquisition, processing and image handling [10, 12, 13, 14, 15]. Conventional CT has been replaced by dynamic thin section CT, spiral CT, multidetector CT (MDCT), and three-dimensional reconstruction.

The criteria predictive for unresectability based upon CT scanning are: 1) extra-pancreatic metastases (hepatic, serosal, or peritoneal); 2) extrapancreatic extension of the tumor beyond bile duct, duodenum or gastric antrum; 3) celiac axis or hepatic hilar lymph nodes; 4) invasion or encasement of the celiac axis, hepatic, or superior mesenteric arteries; or, 5) involvement of the portal or superior mesenteric vein with thrombosis [3, 16]. CT is accurate in assessing extra-pancreatic involvement, but it is limited in assessing local vascular invasion (portal vein and superior mesenteric artery involvement). It is frequently difficult to distinguish whether the tumor is touching vascular structures or actually invading them; a distinction that can often only be made at the time of surgery.

In a study by Velanovich *et al*., the accuracy of conventional CT scanning alone in predicting unresectable disease was 92%, but the accuracy of CT scanning for predicting resectable disease was only 45% [17]. In a similar study by Ross *et al*., the accuracy of predicting unresectable disease was 93%, and the accuracy of predicting resectable disease was 38% [15]. A study by Fuhrman *et al*. has shown that thin section contrast enhanced CT predicted resectability in 88% of patients [16]. Although this study reports a high predictive value of CT scanning in determining resectability, it includes peri-pancreatic malignancies that are known to have a limited incidence of peritoneal metastases.

Several authors have shown spiral CT to be accurate for staging pancreatic cancer and particularly for predicting resectability [18, 19, 20]. Bluemke *et al*., using single-phase spiral CT, correctly predicted resectability in 70% of patients with pancreatic cancer [19]. Diehl *et al*. correctly predicted unresectable disease in 96% of patients and resectable disease in 79% using dual-phase spiral CT [20]. Gmeinwieser *et al*. showed that spiral CT was 93% and 100% accurate in detecting portal venous and arterial involvement, respectively [18].

The current staging test of choice is multi-detector 3D CT scan that allows acquisition of three-dimensional data and imaging of the entire pancreas in a single breath-hold. With reconstruction of overlapping images and elimination of artifacts from movement with inspiration, the detection of small lesions and arterial and venous involvement is markedly improved.

A recent study correlated findings of MDCT with actual resectability determined at surgery in 25 patients. Two patients (8%) were considered not resectable because of vascular invasion which was confirmed in one at surgery. Of the 23 patients deemed resectable by CT, 20 were resected yielding a negative predictive value of 87% (20/23). In these three patients, small metastases to the liver and peritoneum were discovered at surgery [21]. In another recent study, 44 patients underwent thin-section dual-phase MDCT to stage their tumor, followed by open surgery. Of the 44 patients, 23 were resectable. The sensitivity for CT in predicting resectability was 96% (22/23) but the specificity was only 33% (7/21). Only the degree of arterial involvement was a significant predictor of resectability. The authors concluded that even modern CT remains relatively nonspecific for predicting resectability and diagnostic laparoscopy continues to have an important role in staging of pancreatic cancer [22]. Preliminary data involving multi-detector row CT (MDCT) and curved planar reconstruction show that the reformation images are equivalent to the transverse images obtained from MDCT. In a study by Prokesch *et al*., 43 patients underwent MDCT for suspected pancreatic tumors. Subsequently, curved planar reformations were generated along the pancreatic duct, common bile duct, and major mesenteric vessels. The two modalities were then compared for presence of tumor, resectability, and vascular involvement. When assessing the ability to detect pancreatic cancer, MDCT had a sensitivity of 95% and specificity of 90%, compared to reconstruction images of 98% and 91% respectively. For the ability to determine tumor resectability, MDCT had a sensitivity of 86% and specificity of 85%, compared to 71% and 84% respectively for reconstruction images [23].

Although advances in CT have improved the ability to predict resectability, limitations remain including the sensitivity of CT to detect tumors less than 1 cm in diameter, thus limiting the detection of peritoneal metastatic deposits, small liver metastases, and peritoneal micrometastases [24, 25, 26]. CT scan also cannot distinguish between reactive lymphadenopathy and malignant deposits. Concern remains about the potential for a false positive diagnosis of unresectability resulting in an inappropriate denial of surgery and a false positive diagnosis or resectability resulting in an unnecessary trip to the operating room. These limitations can potentially be overcome with the assistance of other imaging modalities particularly diagnostic laparoscopy with the use of laparoscopic ultrasonography and biopsy [27].

Endoscopic Retrograde Cholangio-pancreatography (ERCP)

ERCP is often used as a diagnostic tool in pancreatic cancer but is rarely of any benefit [28, 29]. Most surgeons agree that ERCP is not a useful test in pancreatic cancer. Pre-operative relief of bile duct obstruction is of benefit only when the patient has severe jaundice or cholangitis. It has been clearly shown that preoperative biliary stenting to relieve jaundice is unnecessary in most cases. ERCP to delineate duct anatomy and to obtain cytological brushings may be useful when pancreatic cancer is suspected but no mass is seen on CT [10]. However, a normal pancreatogram does not completely exclude malignancy [24]. The differentiation between chronic pancreatitis and pancreatic cancer can also be difficult on ERCP. In one study, ERCP was misleading in the diagnosis of pancreatic cancer in 13% of patients [30]. Further, diagnostic ERCP always carries the risk of pancreatitis and can induce cholangitis [31, 32] and thus is not recommended as a routine diagnostic test in pancreatic cancer; however, the use of ERCP with biliary decompression is appropriate in selected patients with profound jaundice and hepatic dysfunction or when there will be a delay in surgical treatment.

Magnetic Resonance Imaging (MRI)

Abdominal MRI is rapidly evolving but currently provides essentially the same information as CT scanning [27]. Its initial limitations involve image artifacts from respiration, aortic pulsation, bowel peristalsis, and a lack of ideal contrast material for the gut lumen. Recent advances have improved abdominal imaging with MRI but it has not replaced high-quality CT-scanning at this time. In recent studies from Steiner *et al*., T2-weighted images were comparable with and in 22% of cases superior to the CT scan because it showed a difference in the signal intensity between the tumor and the normal pancreatic tissue [33]. MRI was also slightly superior to CT in visualizing larger tumor masses but overall no significant advantage was offered over a high-quality CT. A prospective study comparing CT, MRI, angiography and EUS in 62 patients determined that CT had the highest accuracy in predicting resectability (83%). The authors suggested that the most cost-effective strategy is to use CT as the initial test followed by other confirmatory techniques in potentially resectable cases [34].

Endoscopic Ultrasonography (EUS)

Endoscopic ultrasound (EUS) can be used to detect small pancreatic masses when there is a high suspicion for pancreatic cancer but no mass is clearly identified by CT scan. With the probe placed in the stomach or duodenum right next to the pancreas, interference from overlying bowel gas is eliminated and allows for higher frequency waves, which improve image resolution [27]. EUS is also a sensitive test for portal vein invasion and is superior to abdominal US and CT in determining tumor size, extent, and lymph node status. EUS is somewhat less effective at detecting superior mesenteric artery invasion. As with all ultrasound applications, EUS of the pancreas is limited by the experience and expertise of the ultrasonographer.

Endoscopic–Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA)

Fine needle aspiration (FNA) can be performed using EUS as a guide. Several authors have reported highly sensitive and specific results for percutaneous FNA with minimal morbidity [35, 36, 37]. Initially there was concern that malignant cells could seed the peritoneal cavity along the needle tract during percutaneous biopsy of pancreatic cancers and EUS-FNA would avoid this problem [38]. However, many biopsies have been performed percutaneously without the appearance of this complication. The role of preoperative EUS-FNA, or percutaneous biopsy, is limited because a negative biopsy does not rule out cancer and does not preclude the need for surgical exploration. However, this technique is very useful if a protocol involving neoadjuvant treatment is under consideration. In expert hands, adequate specimens are obtained in about 95% of cases and the results often expedite therapy and influence clinical decisions [39, 40, 41]. The sensitivity of EUS-FNA is 84% along with a specificity of 96%, giving this technique a reported accuracy of 85% [41].

Cytology

Diagnostic laparoscopy provides the opportunity to obtain peritoneal washings for cytology. This can be helpful as a prognostic indicator because negative cytology is correlated with improved survival even in the presence of metastases [42, 43, 44, 45]. In contrast, positive peritoneal cytology is usually correlated with metastatic disease and poor survival. Peritoneal washings for cytology can easily be performed at the time of diagnostic laparoscopy. However, the results are not available at the time of surgery, which mandates a second anesthetic for this information to be utilized in clinical decision-making regarding need for open exploration. One report indicated that cytology will be positive and exclude 10% of patients from exploration despite a CT and simple laparoscopy (without ultrasound) consistent with resectable disease [46].

Diagnostic Laparoscopy

Computers and microchip technology have led to a trend towards minimally invasive surgery. Modern surgeons strive to manipulate anatomy and provide surgical care in the least invasive method possible. In addition, wide acceptance of laparoscopic cholecystectomy has brought laparoscopic surgery into the mainstream of general surgical practice. These new techniques are now being applied to a wider spectrum of general surgical problems. Most patients with pancreatic cancer have metastatic disease and cannot benefit from surgery. However, even with the advancement of radiographic imaging, it can be difficult to determine which patients are candidates for resection and minimally invasive surgery may help avoid unnecessary diagnostic laparotomies.

Several studies have demonstrated the value of laparoscopy in the staging of abdominal malignancies [3, 9, 10, 11, 47, 48, 49].

Laparoscopic examination allows for direct visualization of intra-abdominal contents and has been reported to identify hepatic and peritoneal metastases that were not shown by other modalities. Diagnostic laparoscopy involves a general exploration of the abdominal surfaces including palpation of the liver with two instruments. The hilum of the liver is visualized and the foramen of Winslow is examined and periportal lymph nodes are biopsied if enlarged. The transverse colon and omentum are reflected cephalad and the base of the transverse mesocolon is examined for tumor with particular attention to the mesocolic vessels. The gastrocolic ligament/omentum is incised and the lesser sac is examined [3].

A critical appraisal of the literature reveals that the percentage of patients with unresectable disease found at diagnostic laparoscopy has decreased over time as the sensitivity of CT scanning has improved. Conlon *et al*. examined 115 patients with pancreatic cancer using abdominal CT and diagnostic laparoscopy [3]. Sixty-seven patients out of 115 were considered to have resectable disease on completion of the laparoscopic examination. A resection was performed in 61 patients, so the correct assessment of resectability was (91%). Six patients (9%) did not undergo resection because of disease that was missed at laparoscopy. In five cases, laparoscopy failed to identify hepatic metastases, and encasement of the portal vein was not appreciated in one patient. Unresectable disease was identified in 41 patients. Open exploration and resection were performed under the same anesthetic upon completion of the laparoscopy. There were no intraoperative or postoperative complications related to the laparoscopic procedure. The positive predictive index, negative predictive index and accuracy of the procedure were 100%, 91% and 94%, respectively. This study showed that use of laparoscopy significantly reduces the percentage of patients undergoing open exploration without resection, with an overall resectability rate of 76%.

In 1998 Merchant and Conlon reported their results using a laparoscopic technique to evaluate 442 consecutive patients with pancreatic and periampullary malignancies [45]. Preoperative radiographic evaluation included a contrast-enhanced CT in all patients (n=420), and selective use of ultrasonography (n=194), ERCP (n=195), and visceral angiography (n=22). Based on this assessment, 339 patients (77%) were considered to have resectable disease with 303 patients subsequently undergoing laparoscopic staging. After laparoscopic evaluation, only 199 patients were still considered to have resectable disease and 104 were determined to be unresectable with findings of liver metastases (n=48), extrapancreatic disease (n=41), nodal disease (n=20), and vascular invasion (n=37). One patient was found to have benign disease. There were 18 patients considered resectable upon laparoscopic exploration, who were not resected during laparotomy. In fact, 181 patients out of 199 (91%) considered resectable after laparoscopic assessment were resected. Of 104 patients considered to be unresectable at laparoscopy, none underwent resection. Consequently the laparoscopic assessment provided a positive predictive index of 100%, a negative predictive index of 91%, and an accuracy of 94%.

Laparoscopic Ultrasonography

Despite the aforementioned results achieved by laparoscopy alone, this procedure still has limitations in the staging of pancreatic cancer, including only two-dimensional inspection of the surface of the liver and the peritoneal cavity and a lack of tactile sensation. These factors limit the identification of small intra-parenchymal hepatic metastases and make it difficult to evaluate the critical retroperitoneal tumor-vessel relationships [45, 50]. Laparoscopic ultrasound (LUS) probes offer a possible solution allowing the surgeon to examine the liver, the porta hepatis, and the portal vein and superior mesenteric artery. Diagnostic laparoscopy with the use of ultrasound improves the accuracy of predicting resectability up to as high as 98% in some studies [50, 51, 52, 53, 54].

Bemelman *et al*. staged seventy patients with pancreatic cancer with laparoscopy and LUS. Twenty-one patients were found to have metastatic disease. Of 49 patients undergoing laparotomy, 21 of 22 considered resectable after LUS examination were resected. Also, 6 of 13 patients that were considered "probably resectable" as well as 2 of 14 that were deemed unresectable, were, in fact, resected. The overall sensitivity and specificity for determining resectability were 67% and 96%, respectively. Unnecessary laparotomy was avoided in 14 patients (19%) and the therapeutic approach was changed in 18 patients (25%) using the combination of laparoscopy and LUS [55].

John *et al*. evaluated 40 patients with potentially resectable pancreatic cancer [51]. Metastatic disease was identified with laparoscopy alone in 14 patients (35%). The addition of LUS revealed factors that increased the number of patients deemed unresectable (59%). The overall accuracy in predicting resectability with the addition of LUS was 89% compared with only 65% with laparoscopy alone.

Merchant and Conlon reported a prospective evaluation of 90 patients with pancreatic tumors undergoing laparoscopy with LUS [45]. Conventional imaging techniques such as CT scan identified 65 patients as being resectable, 17 as unresectable, and 8 as equivocal. Laparoscopy showed 36 patients to be resectable, 13 to be equivocal and 41 to be unresectable. The use of LUS in addition to laparoscopy revealed a primary tumor in 88 patients, involvement of the portal vein in 87 patients, the superior mesenteric vein in 85 patients, and the hepatic and superior mesenteric artery in 84 patients. LUS confirmed the resectable and unresectable cases determined by laparoscopy alone. Of 13 patients with equivocal findings at laparoscopy, LUS identified 8 with unresectable disease. Five patients with equivocal findings at laparoscopy were considered resectable with LUS. Four of those underwent resection and only one was found to be unresectable because of celiac axis involvement not identified by LUS. Taken all together, this study provided a positive predictive index of 100%, a negative predictive index of 98%, and an accuracy of 98% in determining resectability.

Initial CT scans obtained in patients with pancreatic cancer often are of a suboptimal quality and therefore do not properly reveal metastatic disease that would be evident on a high-quality CT scan. In some studies, diagnostic laparoscopy with the use of ultrasound improves the accuracy of predicting resectability to about 98% [50, 51, 53, 54]. The true yield of laparoscopy cannot be assessed from studies that do not use a state of the art CT scan prior to laparoscopy. Advances in the quality of preoperative imaging have led to accurate radiographic prediction of resectability in at least 80% of cases. This fact does diminish the usefulness of laparoscopy and LUS as a routine diagnostic technique prior to laparotomy (particularly if performed under separate anesthesia) [56].

Clinical data suggests that laparoscopy may be important in the prevention of unnecessary laparotomy in selected patients that are at higher risk for contraindications to resection despite a CT scan consistent with resectable disease [50]. Selective use of staging laparoscopy may be of benefit to avoid a non-therapeutic laparotomy in up to 13% of patients that come to surgery for pancreatic cancer. The addition of LUS during laparoscopic staging enhances the ability of laparoscopy to determine resectability of these tumors. The experience at the Massachusetts General Hospital with staging laparoscopy and peritoneal cytology over an 8-year period in 239 patients indicates that approximately 30% of patients without metastases by CT harbor occult metastatic disease detectable at laparoscopy [46]. Currently, there is no data addressing factors found on a CT scan or clinically that will predict a positive laparoscopy in conjunction with LUS. However, we would suggest that patients with a tumor measuring greater than

4 cm, tumors found in the body or tail of the pancreas, weight loss greater than 9 kg, hypoalbuminemia, or a markedly elevated CA 19-9 would suggest a positive laparoscopy with LUS. In some studies, the accuracy of laparoscopy in combination with LUS for the assessment of resectability approaches that of open laparotomy without significantly increasing morbidity or mortality.

Conclusion

In 2005, the accuracy of CT scanning in predicting resectability in patients with pancreatic cancer has improved to about 90%. Approximately one in ten patients brought to the operating room with the intent of a curative resection will be found at the time of surgery to have unresectable cancer. Diagnostic laparoscopy is more sensitive than CT in detecting small superficial liver and peritoneal metastases. As with all ultrasound techniques, laparoscopic ultrasound is limited by the skills of the ultrasonographer. However, in experienced hands, it seems to improve the detection of intraparenchymal liver metastases and involvement of the portal vein, superior mesenteric vein and superior mesenteric artery. The addition of peritoneal washings for cytology improves the detection of stage IV disease but this requires the laparoscopic examination to be performed under a separate anesthetic. The increased costs of diagnostic laparoscopy with laparoscopic ultrasound cannot be justified for the small subset that will benefit from its routine use. A selective use in cases where detection of unresectable disease is more likely seems to be a rational approach. Factors that suggest a higher yield with diagnostic laparoscopy include a large primary tumor (greater than 4 cm), a tumor in the body or tail of the pancreas, equivocal findings of metastasis on CT, the presence of ascites, severe weight loss (greater than 9 kg), hypoalbuminemia, and a markedly elevated CA 19-9.

The ability of minimally invasive surgeons and endoscopists to diagnose and palliate unresectable pancreatic cancer is likely to continue to improve and these techniques will play an increasingly important role in the care of patients with pancreatic cancer. Likewise, the accuracy of radiological imaging techniques to detect unresectable disease will also continue to advance and further decrease the incidence of nontherapeutic laparotomies. Thus, the optimal application of conventional surgery and minimally invasive approaches for the diagnosis and palliation of pancreatic cancer will continue to evolve.

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Abbreviations LUS: laparoscopic ultrasonography; MDCT: multidetector computed tomography

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