Role of staging laparoscopy in peri-pancreatic and hepatobiliary malignancy

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Abstract

Even after extensive preoperative assessment, staging laparoscopy may allow avoidance of non-therapeutic laparotomy in patients with radiographically occult metastatic disease. Staging laparoscopy is associated with decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy compared to laparotomy but its yield has decreased with improvements in imaging techniques. Current uses of staging laparoscopy include the following: (1) In the staging of pancreatic adenocarcinoma, laparoscopic staging allows for the identification of sub-radiographic metastatic disease in locally advanced cancer in approximately 30% of patients and, in radiographically resectable cancer, may identify metastatic disease in 10%-15% of cases; (2) In colorectal liver metastases, selective use of laparoscopic staging in patients with a clinical risk score of over 2 identifies unresectable disease in approximately 20% of cases; (3) In hepatocellular carcinoma, laparoscopic staging could be selectively used in high-risk patients such as those with clinically apparent liver cirrhosis and in patients with major vascular invasion or bilobar tumors; and (4) In biliary tract malignancy, staging laparoscopy may be used in all patients with potentially resectable primary gallbladder cancer and in selected patients with T2/T3 hilar cholangiocarcinoma. Because of the decreasing yield of SL secondary to improvements in imaging techniques, staging laparoscopy should be used selectively for patients with pancreatic and hepatobiliary malignancy to avoid unnecessary non-therapeutic laparotomy and to improve resource utilization. Each individual surgeon should apply his or her threshold as to whether staging laparoscopy is indicated according to the quality of preoperative imaging studies and the availability of resources at their own institution.

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INTRODUCTION

Resection remains the only treatment that can lead to cure and long-term survival in patients with peri-pancreatic or hepatobiliary malignancy. The majority of these patients, however, will present with metastatic disease and surgical resection in this setting is generally contraindicated. Despite continuous improvements in preoperative staging techniques, some patients will present with radiographically occult metastatic disease and will be identified with locally unresectable or metastatic disease at the time of operation.
Staging laparoscopy (SL) has been proposed as a minimally invasive technique for the identification of radiographically occult metastatic or locally unresectable disease. The benefit of this approach is in avoidance of non-therapeutic laparotomy. SL, in comparison to non-therapeutic laparotomy, has been reported to result in decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy[8]. Previously published work by our group[9] reported that laparoscopic staging compared to laparotomy did not significantly increase the operative time (83 ± 22 min vs 91 ± 33 min) but significantly decreased length of hospital stay (2.2 ± 2 vs 8.5 ± 8.6) and the total hospital charge. Controversy over the use of SL exists because the yield of this approach has decreased as imaging techniques have improved. The yield of SL is directly related to the quality of imaging as well as the likelihood that a given lesion will metastasize.

The aim of this report is to review the current yield of SL and assess the role and indication of SL in peri-pancreatic and hepatobiliary malignancy with a special attention to pancreatic cancer, colorectal liver metastasis, hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer.

**LAPAROSCOPIC TECHNIQUE**

The yield of laparoscopic staging depends on the quality of preoperative imaging studies and also the thoroughness of the laparoscopic technique. Briefly, and as previously reported by our group[10], SL is performed under general anesthesia typically at the time of planned resection. A 10 mm trocar is inserted under direct vision along the anticipated laparotomy incision. Under 15 mm Hg pressure pneumoperitoneum, the abdomen is evaluated with a 30° angle laparoscope. The whole abdomen is inspected including the parietal and visceral peritoneum from every quadrant, the pelvis, the anterior and posterior surface of the liver, the porta hepatitis, the gastrohepatic omentum, the duodenum, the transverse mesocolon and celiac region. Typically, two additional 5 mm ports are necessary for exposure. Any lesions likely to be metastases are sampled and analyzed by frozen section. When no metastatic lesions are found or if there is doubt about locally advanced disease, laparoscopic ultrasound can be performed using 7.5 MHz flexible probe placed through a 10-mm port. Ultrasonic examination of the whole liver (including hepatic vein, portal pedicle with a special attention to hepatic artery, portal vein or biliary involvement), lymph nodes and superior mesenteric artery can be readily performed.

SL has its greatest yield in the identification of superficial metastatic disease and is less accurate in identifying deep liver metastases, local vascular involvement or lymph node metastases. Some have advocated the routine use of laparoscopic ultrasonography to enhance the accuracy of the staging procedure with respect to the primary tumor relationship to the major blood vessels, the presence of enlarged peripancreatic lymph nodes or small deep liver metastasis[11]. In this setting, laparoscopic ultrasonography may identify additional disease in approximately 10% of patients[11] but whether it should be routinely or selectively used is controversial. Laparoscopic ultrasound probes are not widely available and thus the surgeon’s familiarity with the findings is limited.

**ISSUE OF PORT-SITE RECURRENTCE**

Initial reports of laparoscopy in cancer patients expressed concern about the oncological safety of laparoscopy with special attention to port-site recurrence and oncological outcome. Large series of oncological laparoscopic procedures have now been reported including randomized data in colon cancer[12] that have confirmed the safety of this approach with respect to disease recurrence and disease-specific survival. The rate of port-site recurrence does not seem to differ from the rate of incisional recurrence observed after open exploration for cancer. This has been specifically studied in laparoscopic staging for pancreatic cancer and has not been found to be associated with an increased risk of port-site recurrence or peritoneal progression[9,10]. Overall, no difference in survival has been observed between patients with pancreatic cancer who had a diagnostic procedure but no pancreatic resection with or without a laparoscopic approach[10].

**OVERALL MORBIDITY AND MORTALITY**

The overall reported mortality of SL is < 1% and the reported morbidity is very low with the majority of reported complications minor and usually related to the general health status of the patient. Potential complications due to the laparoscopic procedure include general surgical complications such as port-site bleeding, wound infection and the general risks associated with a general anesthetic. The most significant risk is from a missed colonic or small bowel injury occurring at the time of port insertion or during adhesiolysis from previous surgery and care must be taken during SL to evaluate for these injuries.

**STAGING LAPAROSCOPY IN PANCREATIC MALIGNANCY**

**Adenocarcinoma**

Accurate staging is essential in the treatment planning for patients with pancreatic cancer. Non-invasive staging has seen a dramatic improvement over the past few decades with improvements in cross-sectional imaging techniques. Since the purpose of SL is to supplement and not replace non-invasive imaging techniques, extensive preoperative assessment remains mandatory. As recently stated in an expert consensus statement[11], the current state-of-the-art imaging modality is multidetector CT with advanced volumetric processing techniques. In the case of equivocal imaging, magnetic resonance imaging may be considered but has not demonstrated a clear advantage over CT[12]. Endoscopic ultrasound (EUS) may also be useful for the evaluation of local resectability however it has been the authors’ expe-
rience that EUS may over interpret the extent of vascular involvement and triple-phase CT imaging is considered the most accurate in assessment of the local vasculature. Recently, FDG-PET/CT has been advocated to be more sensitive than conventional imaging in the diagnosis of both primary and metastatic pancreatic adenocarcinoma and may be warranted in the high-risk patient to rule out radiographically occult or equivocal stage IV disease.

Laparoscopic staging: Even in the setting of high-quality preoperative imaging, up to a third of patients will be found to have radiographically occult distant metastatic or locally unresectable disease at the time of SL. To decrease patient discomfort and potential morbidity due to exploratory laparotomy, SL for this disease has been advocated since 1978 when Cuschieri reported his experience of 23 cases of pancreatic cancer. Despite this relatively high yield for SL, the indications for SL have not been widely accepted and continue to evolve as the ability to non-invasively identify disease stage evolves. Table 1 presents the main studies assessing the role of SL in pancreatic cancer.

The initial report from our institution of 115 patients undergoing SL for radiographically resectable pancreatic and peripancreatic malignancy included patients evaluated between 1992 and 1994. Adequate SL was feasible in 94% of patients and findings that precluded resection were found in 38% of patients. Findings included liver metastasis (50%), extrapancreatic peritoneal disease (39%), vascular encasement (35%) and celiac or portal lymphatic metastasis (20%). In 9% of patients who were deemed resectable by SL, there was disease identified at laparotomy that rendered the patient unresectable. In this series, there was no peri-operative complications reported to SL. At the time this study was performed, the positive predictive index, negative predictive index and accuracy of SL were 100%, 91% and 94% respectively.

With improvements in cross-sectional imaging and evaluation, we believe that the current yield of SL for peripancreatic and pancreatic malignancy has decreased. We recently reported an updated review of 1045 patients who had undergone SL between 1995 and 2005. The yield of SL for pancreatic malignancy in this more contemporary series was 14%. Factors associated with radiographically occult unresectable disease included SL performed before 1999 (the year that multi-detector CT became available at our institution), imaging not performed at our institution, pancreatic primary site, adenocarcinoma (vs other type of tumor) and symptoms (weight loss, jaundice). Primary site (pancreatic versus nonpancreatic) was identified as the strongest predictor of yield. In patients with nonpancreatic tumors, the yield of laparoscopy was 4% vs 14% in patients with pancreatic tumors. Because of these findings, our general approach toward SL for these disease sites is to routinely generally perform SL only in patients with pancreatic adenocarcinoma.

The results noted above highlight the need to identify factors associated with the likelihood of subradiographic metastatic disease. This likelihood is inversely proportional to the quality of imaging (higher quality imaging, lower likelihood of subradiographic metastatic disease) and proportional to the biology of the disease (increased metastatic potential, increased likelihood of subradiographic metastatic disease). Through an awareness of the quality of imaging and an understanding of the biology of the specific disease, the surgeon can have a better estimate of the yield of SL in the individual patient. With this knowledge, the surgeon may then utilize SL at whatever threshold they feel is beneficial. Some surgeons may feel SL is warranted if the likelihood of subradiographic disease is 5%, others 10%, but only with an understanding of the yield of SL can surgeons appropriately utilize this procedure.

In 2005, Karachristos et al. reported on the relationship between CA 19-9 and the likelihood of subradiographic metastatic disease. In their study, patients with higher CA 19-9 levels had significant higher odds of having metastasis identified by laparoscopy (odds ratio, 1.83; \( P = 0.04 \)) and no patient with a CA 19-9 level below 100 U/mL had metastatic disease identified during SL. Similar results have been reported from our group in a study of 491 patients in which a CA 19-9 over 130 U/mL was associated with sub radiographic unresectable pancreatic adenocarcinoma in 26% of patients vs 11% when CA 19-9 was below 130 U/mL. CA 19-9 when combined with the previous factors identified, i.e. nonpancreatic primary site, adenocarcinoma (vs other type of tumor), weight loss and jaundice, may provide an improved ability to identify subgroups of patients both at very high-risk and at very low-risk for subradiographic metastatic disease. In patients at very high-risk of subradiographic disease, SL alone may be warranted with the anticipation that resection would be scheduled only in those patients with negative findings. In patients at very low-risk for subradiographic disease SL may not be indicated.

| Study/years | Time period | No. of patient | Contraindication found during laparoscopy (%) | Contraindication found during laparotomy (%) | Morbidity/ Mortality of LAP | Note |
|-------------|-------------|----------------|---------------------------------------------|---------------------------------------------|----------------------------|------|
| Conlon et al, 1999 | 1992-1994 | 115 | 38 | 8 | 0/0 | Extended laparoscopy only |
| Jimenez et al, 2000 | 1994-1998 | 125 | 31 | 3 | 0.8/0 | + cytology |
| Schachter et al, 2000 | 1996-1999 | 67 | 45 | 12 | - | + LAPUS |
| Doran et al, 2004 | 1997-2002 | 305 | 15 | 20 | - | + LAPUS |
| Maithel et al, 2008 | 2000-2006 | 491 | 14 | 1.5 | - | + CA 19-9 |

*On remaining patients; 1On metastatic spread only. LAPUS: Laparoscopic ultrasonography; LAP: laparoscopic staging.
Peritoneal cytology performed at the time of SL has also been reported as a minimally invasive approach to identify sub-radiographic metastatic disease. The current AJCC classification stages positive peritoneal cytology as stage IV disease with median survival reported between 6 and 12 mo. Positive cytology rates in those presenting with radiographically resectable disease vary and range from 3% to 10% of cases. In our experience, patients who have undergone resection in the setting of positive peritoneal cytology and absence of other identifiable metastatic disease had a similar survival as patients with stage IV disease. Nevertheless, the utility of peritoneal cytology remains controversial and, overall, many remain reluctant not to perform resection when the tumor is resectable and without macroscopic metastatic disease.

Overall, it is difficult to precisely assess the sensitivity, specificity, positive and negative predictive value of SL for pancreatic and peri-pancreatic malignancy as studies are not easily comparable due to various approaches for pre-operative imaging (and their constant improvement) and intraoperative assessment (cytology, laparoscopic ultrasonography, etc.). As stated in a recent expert consensus statement, laparoscopic staging could be selectively used in locally advanced pancreatic cancer and in apparent resectable cancer localized in the pancreatic body or tail and larger than 3 cm with equivocal findings on CT scan or in the setting of a high CA 19-9 level (> 100-200 U/mL). Given our findings of an overall yield of 14% in patients with pancreatic adenocarcinoma, it is our general approach to perform SL on all patients with pancreatic adenocarcinoma and selectively in patients with peri-ampullary malignancy.

**Endocrine and other tumors**

The yield of SL in patients with pancreatic endocrine neoplasms has not been clearly reported. In the report from our institution noted above, we found that the overall yield of laparoscopy was 8% in non-adenocarcinoma tumors (endocrine tumor, mucinous cystic and Intraductal Papillary Mucinous Neoplasms). This yield was significantly less than in patients with pancreatic adenocarcinoma. In patients with pancreatic endocrine tumors, distant metastases do not necessarily contraindicate resection and therefore SL should be used in selected patients where findings of radiographically occult metastatic disease would alter the operative approach.

**STAGING LAPAROSCOPY IN HEPATOBIARY MALIGNANCY**

Similar to pancreatic cancer, operative resection in hepatobiliary malignancy is associated with improved survival only in selected patients in which complete tumor resection can be performed with an adequate hepatic remnant for recovery. The presence of sub-radiographic metastatic disease is also of concern in certain patients with hepatobiliary malignancy. In a study by D’Angelica et al. of 410 patients with radiographically resectable hepatobiliary malignancy, SL was completed in 73% of patients and, in 84 (55%) of the 153 evaluated patients, SL identified disease that precluded resection. In this group of patients, SL was valuable in identifying unsuspected cirrhosis, peritoneal disease and additional hepatic tumors but it commonly failed to identify extra-regional lymph node metastases and vascular invasion. The addition of laparoscopic ultrasonography identified clinically important additional disease in 4.8% of patients and was responsible for approximately 10% of the findings of unresectability. In this study, laparoscopy spared one in five patients a laparotomy while reducing hospital stay and morbidity.

**Liver metastasis**

**Colorectal:** The decision to perform hepatic resection in patients with metastatic colorectal cancer to the liver remains challenging and SL with or without addition of ultrasonography has been advocated as a minimally invasive approach to identify those with liver confined and resectable disease. Initial publications in the 1990s identified SL with intraoperative ultrasonography of the liver as a valuable tool to assess the resectability of hepatic metastases. In the setting of radiographically resectable metastatic colorectal disease, Rahusen et al. reported a 38% yield of SL with intraoperative ultrasonography. Later, those results were confirmed by Thaler et al. who identified a 25% yield of SL in identifying radiographically occult disease which led to the decision of resection or no resection.

Limitations of the use of SL with laparoscopic ultrasonography for metastatic colorectal cancer often include extensive adhesions following previous primary surgery and again the ability to thoroughly and accurately assess the liver with laparoscopic ultrasound. The study of segment VII and VIII seems more difficult with laparoscopic ultrasound compared to open ultrasonography even after division of the falciform ligament. Similarly, definitive evaluation of the caudate lobe and retroperitoneal lymph nodes remains challenging. Even if laparoscopic ultrasound is added, the yield in the detection of nodal disease seems to be comparable to laparoscopy alone.

Laparoscopic staging should be considered the first step of a laparoscopic liver resection. Indeed, laparoscopic liver resection is now increasingly utilized and studies from several centers attest to its technical feasibility and safety with oncological results comparable to open resection. Recent international consensus positions such as the Louisville Statement have stated laparoscopic liver surgery as a safe and effective approach to the management of surgical liver disease. It now seems possible to perform laparoscopic major hepatectomy following SL.

With optimal preoperative evaluation including ultrasound, modern triphasic helical CT and MRI, the yield of laparoscopic staging has decreased and the majority of patients with potentially respectable hepatic colorectal metastasis may not benefit from SL. We previously reported that the yield of laparoscopic staging was lowest for metastatic colorectal cancer compared to other hepatobiliary malignancies. These data suggest that a selective approach to SL in these patients may improve resource allocation.
Estimates have suggested the use of SL has been limited. However, the accuracy of SL was decreased in tumors > 10 cm in patients with unresectable disease. In their experience, the accuracy of SL was decreased in tumors > 10 cm in patients with unresectable disease. In this study, the yield of laparoscopy was more important in gallbladder cancer 

Non colorectal metastases: Estimates have suggested that half the number of liver metastasis from neuroendocrine tumors are undetectable on preoperative imaging despite extensive imaging. SL with ultrasonography could be performed at the first step of the intervention to rule out additional metastatic disease. Nevertheless, due to the indolent nature of these tumors and the association between cytoreduction and long-term survival, SL to exclude additional disease may not result in a change in management. Therefore we do not routinely perform SL prior liver resection for liver metastasis from neuroendocrine tumors.

Primary hepatic malignancy

Hepatocellular carcinoma: The use of SL has been advocated to select patients with hepatocellular carcinoma for resection. The literature evaluation of SL for hepatocellular carcinoma is not as extensive as for other malignancies. Peritoneal spread is relatively rare in hepatocellular carcinoma, however, the risks of laparotomy in patients with altered liver function subject to postoperative ascites should be considered as increasing the potential benefit of SL. In addition to tumor assessment, SL in patients with hepatocellular carcinoma provides a minimally invasive assessment of the severity of cirrhosis and the size of the liver remnant which is critical for the assessment of resectability. Lo et al reported that SL and laparoscopic ultrasonography allowed for the avoidance of laparotomy in 63% of patients with unresectable disease. In their experience, the accuracy of SL was decreased in tumors > 10 cm and in the evaluation of tumor thrombi in major vascular structure and/or the invasion of adjacent organs. In patients who were spared laparotomy, a faster postoperative recovery and an earlier initiation of nonoperative treatment was observed and the authors suggest that the procedure should be performed routinely before laparotomy for hepatocellular carcinoma. Our group has proposed a more selective approach and generally recommends SL only in high-risk patients such as those with clinically apparent liver cirrhosis and in patients with major vascular invasion or bilobar tumors. Table 3 presents the main studies assessing the role of SL in hepatocellular carcinoma.

Biliary malignancy: Preoperative assessment of resectability of biliary tract tumors is challenging since, in addition to metastatic spread, the resectability of a given tumor is predicated on hilar vascular and biliary involvement which is often not accurately assessed by preoperative imaging. Despite extensive preoperative evaluation, less than half of patients who undergo exploration are amenable to a potentially curative resection and the issue of resectability is usually resolved at laparotomy, often after an extensive dissection of the portal vascular and biliary structures. The exact yield of SL is difficult to assess for cholangiocarcinoma since it depends on the quality of preoperative assessment as well as the willingness to attempt resection based on the surgeon’s experience.

In the Beaujon experience, SL avoided unnecessary laparotomy in a third of patients with potentially resectable biliary carcinoma who had undergone extensive preoperative imaging. Nevertheless, contraindications found during laparoscopy were mainly due to peritoneal and liver metastasis and vascular and lymph node invasion were not diagnosed well by this procedure. The authors concluded that the yield of SL was more important in gallbladder cancer and in intrahepatic cholangiocarcinoma than in hilar cholangiocarcinoma where non-resectability is mainly due to vascular and biliary involvement that is best assessed after dissection.

Similarly, in the MSKCC experience, Jarnagin et al in a prospective analysis of SL of 186 patients with primary and secondary hepatobiliary malignancies found that laparoscopy failed to identify non-resectability because of lymph node metastases, vascular involvement or extensive biliary involvement. Nevertheless, in 100 patients with extrahepatic biliary carcinoma prospectively analyzed, they reported that SL identified the majority of patients with unresectable disease. In this study, the yield of SL as

| Study/years | Time period | No. of patient | Contraindication found during laparoscopy (%) | Contraindication found during laparotomy (%) | Morbidity/Mortality | Note |
|-------------|-------------|----------------|---------------------------------------------|---------------------------------------------|---------------------|------|
| Rahusen et al 1999 | 1991-1997 | 50 | 38 | 13 | /0 | + LAPUS |
| Jarnagin et al 2001 | 1997-1999 | 104 | 14 | 13 | NA | |
| Grobmyer et al 2004 | 1997-2002 | 264 | 10 | 8 | NA | |
| Thaler et al 2005 | 1996-2004 | 136 | 25 | 11 | 2%/0 | + LAPUS |
| Mann et al 2007 | 2000-2004 | 200 | 20 | 17 | NA | + LAPUS |

LAPUS: Laparoscopic ultrasonography.
Biliary tract cancer, especially hilar cholangiocarcinoma, is more likely to be locally invasive and having a slightly longer survival. Nevertheless, the use of laparoscopic ultrasonography increased the yield laparoscopic of staging from 24.3% to 41.5% as reported by Connor et al.[42]. But this remains controversial since Tilleman et al.[43] reported a very limited value of laparoscopic ultrasound in patients with malignant proximal bile duct obstruction. In our experience, laparoscopic ultrasound does not detect any patient with unresectable disease that was not already found at laparoscopy and the interpretation of the findings is often difficult to interpret. Table 4 presents the main studies assessing the role of SL in biliary tract tumors.

CONCLUSION

Even after extensive preoperative assessment, SL may allow for avoidance of non-therapeutic laparotomy in patients with radiographically occult metastatic or locally unresectable disease. Laparoscopy is associated with decreased postoperative pain, a shorter hospital stay and a higher likelihood of receiving systemic therapy compared to laparotomy without significantly increasing the operative time. The yield of SL has decreased with improvements in preoperative imaging techniques. Currently, to improve resource utilization, SL should be used selectively for patients with pancreatic and hepatobiliary malignancy to avoid unnecessary non-therapeutic laparotomy.

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