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TOPIC HIGHLIGHT

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Laparoscopic staging in hilar cholangiocarcinoma: Is it still justified?

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Abstract

Radical resection remains the only potential curative therapy for hilar cholangiocarcinoma (HCCA). The aim of staging laparoscopic (SL) is to identify patients with previously undetected advanced disease who will not benefit from surgical palliation and therefore avoid unnecessary laparotomies. The accuracy of non-invasive imaging techniques has significantly improved during the last years. As a consequence, the diagnostic yield of SL of biliary tract malignancy should have decreased proportionally. At the same time, some authors have recently questioned the value of laparoscopic ultrasound (LUS) as a complement of SL. In this setting, the precise role of SL and LUS in the preoperative workup of HCCA remains unclear. As it seems undoubtedly clear that its efficacy has decreased in the last decades, there is a general consensus that the universal use of SL shouldn't be recommended anymore; SL should be performed only in selected patients with higher risk of holding unresectable disease (T2/T3 or Bismuth type 3/4 and patients with suspicion of metastases). It would also be recommended in patients with potentially resectable disease who would need preoperative invasive procedures. Finally, SL should be performed preceding laparotomy in one session. Further studies on the benefit of SL and LUS in this subset of HCCA patients are warranted.

Key words: Hilar cholangiocarcinoma; Laparoscopy; Staging laparoscopy; Laparoscopic ultrasound

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INTRODUCTION

Radical resection, with an *en bloc* partial hepatectomy in most cases, remains the only potential curative option[1-3] for patients with hilar cholangiocarcinoma (HCCA).

Staging laparoscopy (SL) is a quick and safe minimally invasive investigation that helps to determine the presence of peritoneal disease and occult dissemination within the liver. The addition of direct contact laparoscopic ultrasound (LUS) provides the ability to assess further the local stage of the disease and to evaluate the presence of liver metastases[4].

The accuracy of non-invasive imaging techniques is continuously improving. This improvement has resulted in highly accurate staging for many hepato-pancreato-biliary malignancies, and so, its use is nowadays recommended in selected patients. As an example, the use of SL/LUS appears to be useful as an adjunct in the preoperative staging of patients with resectable colorectal liver metastases, when peritoneal disease is suspected[5]. With regard to pancreatic cancer, the routine use of SL is not warranted any more. Instead, different studies have

determined criteria to identify the subset of patients at high risk for extended disease[6,7] in which LS still has a beneficial yield.

In spite of all the advances in preoperative imaging, evaluation of HCCA remains a challenge. Furthermore, it is not yet clearly stated whether SL should be used routinely in HCCA, or, if selectively, when.

In a recent study from the Memorial Sloan Kettering Cancer Center (MSKCC), with 380 patients, 295 were considered to have resectable disease and underwent surgery. Nevertheless, from these 295 patients that underwent exploration with curative intent, only 157 (53.2%) underwent a potentially curative resection, and ultimately only 120 (40.6%) underwent a R0 resection[8]. In this series SL was performed in patients with high risk of advanced disease, but, in spite of this approach, there was still a high rate of unnecessary laparotomies.

The purpose of this article is to review and update the available evidence to determine the precise role of SL in the diagnostic evaluation of HCCA.

TECHNIQUE

The use of SL for optimizing resectability in HCCA has been reported from the early beginnings of laparoscopy, and naturally, the technique differs from one to another author[4,9-11]. Below is summarized a standard approach.

Simple laparoscopic staging

SL generally begins with two trocars. A third trocar is frequently inserted to help in the inspection or biopsy procedure. The sites of the trocar insertion are usually chosen within the line of the planned incision should the disease be found resectable by laparoscopic assessment[12].

After insertion of the first port, whether by open or closed technique, pneumoperitoneum is established, and a first general inspection performed. A second trocar is inserted, generally in the right mid-quadrant, and a careful inspection of the peritoneum is performed paying particular attention to the diaphragm, falciform ligament, liver (superior and inferior surface), porta hepatis and lesser omentum. Also pelvis is inspected, and by retracting the greater omentum, the small bowel and mesenteric root can be visualized. Any suspicious lesion is biopsied and sent for frozen section analysis[4,9]. If SL reveals previously undetected evidence of unresectability, the procedure terminates here. In any case, a sample must be taken and malignity must be histologically confirmed.

LUS

LUS was soon added to SL with the objective of increasing the sensitivity of the exploration[9-11], and is nowadays routinely used in many centers.

There are several flexible-tip high-resolution types of transducers available and they usually enter through a 10 mm trocar. If needed to allow images in different planes, it can be inserted trough different placed ports (and even occasionally is useful to insert an additional trocar).

A systematic scanning of the liver should be performed in order to rule out possible intrahepatic metastasis. They can appear as hyper, iso or hypoechoic lesions, and therefore, any suspicious lesion should be biopsied under ultrasound control[4]. After this, careful identification of the structures including the primary tumor in the porta hepatis is mandatory. If the quality of the study is not good enough due to inadequate probe contact, the right upper quadrant can be filled with saline solution until hepatic pedicle is covered. Another possible manoeuvre is to release the neumoperitoneum almost completely. This will help to assess the local extension of the tumor and the presence of lymph node metastases. Vascular invasion is suggested if there is loss of planes between the tumor and surrounding vessels. Metastatic lymph nodes are not well circumscribed and hypo-echoic[4]. Simply enlarged nodes may not be invaded by tumor and therefore its malignity should be confirmed by histogical study.

Patients with no evidence of disseminated disease after LS + LUS undergo laparotomy and resectability is again evaluated. At some institutions, diagnostic laparoscopy and laparotomy have to be performed in two differents sessions for logistic reasons[13].

Findings and resectability

The concept of resectability in HCCA related to technical and oncologic variables has evolved with time and may vary from center to center[2,3,8,14].

It is beyond the scope of this article to determine or discuss the concept of resectability for HCCA, but as a general rule it is considered according to the criteria defined by the MSKCC group[1,15]. In their studies, tumors were considered unresectable if any of the following conditions were present before surgery or at laparoscopy or laparotomy: peritoneal metastases; discontinuous intrahepatic metastases; involved lymph nodes in the periduodenal, retropancreatic, common hepatic, or celiac nodal basin; locally advanced disease secondary to main portal vein encasement or tumor extension to second-order biliary radicals bilaterally; or unilateral tumor extension to secondary biliary radicals with contralateral lobar atrophy or contralateral portal vein involvement. The presence of involved proximal porta hepatis lymph nodes is not a contraindication to resection. In addition, selected patients undergoing exploration with involvement of the portal vein generally undergo hepatectomy with resection of the portal vein.

AVAILABLE EVIDENCE

There are not randomized trials that set the role of LS or LUS in the detection of unresectable disease in HCCA. Operable HCCA is not a common condition, and therefore the studies generally extent for long periods of time.

Table 1 summarizes the results of those studies assessing the efficacy and accuracy of SL in detecting unresectable disease in HCCA. In those series that include other kind of tumors, only the subset of patients with

Table 1 Available studies assessing the efficacy and accuracy of staging laparoscopy in detecting unresectable disease in hilar cholangiocarcinoma

Ref.	*n*	LUS (yes/no)	Efficacy	Overall yield	Accuracy	Patients resected *n* (%)	Histology (yes/no)	Morbidity/ mortality	Period of study
Tilleman *et al*[13]	110	Yes	41.8%		72%	35 (86)	Yes	3%/0%	1993-2000
Weber *et al*[15]	56	Yes	25%	Whole series: 25% -T1: 9% (2/23) -T2/T3: 36% (12/33)	42% (14/33)	23 (41)	Yes	-	1997-2001
Goere *et al*[16]	20	No	25%	25% (5/20)	45% (5/11)	9 (45)	Yes	6%/0%	2002-2004
Connor *et al*[17]	84	Yes	24% (SL) 41.5% (+ LUS)		53%	20 (27)	Yes	-	1992-2003
Ruys *et al*[18]	175	No	14%		32%	89 (51)	Yes	-	2000-2010

LUS: Laparoscopic ultrasound; SL: Staging laparoscopic.

HCCA was selected[15,16]. Final diagnostic was confirmed by pathology after resection or by biopsy if tumoral extension was found in all the patients of all referred series[13,15-18]. In spite of all diagnostic tools used preoperatively and after undergoing SL ± LUS, only 30%-50% of the patients were ultimately amenable to a potentially curative resection.

The efficacy and accuracy of the SL seems to have decreased throughout the years: from 41% to 72% respectively in the 2002 report by Tilleman *et al*[13] to 14% and 32% in the most recent report that was published by Ruys *et al*[18] in 2011, although in this study LUS was not performed.

With regard to the LUS, Connor *et al*[17] found in 2005 that the addition of ultrasonography increased the yield of the exploration from 24% to 41.5%. Nevertheless there is not a consensus about its use, and in some recent series LUS is not routinely used[16,18].

The group of the MSKCC analyzed specific subgroups of patients with HCCA in an effort to identify patients with high risk of holding occult unresectable disease. In this study, accrued over a relatively short period of time (4 years) patients were classified according to a preoperative T stage system[1]. They found that the yield of SL was greater (36%) in T2-T3 tumors than in T1 tumors (9%)[15].

Finally, there are no mortality cases reported, and morbidity-when reported-is low (3%-6%).

PRESENT AND FUTURE OF SL IN HCCA

Preoperative evaluation of any stenosis or tumour mass at the hepatic confluence remains a significant challenge despite continuous improvements in non-invasive radiological techniques. It is sometimes difficult to differentiate between gallbladder cancer (GBC) and HCCA: in a cohort of 110 patients with supposed proximal bile duct obstruction there was doubt about the localization of the tumour in at least 20% of the cases[13]. But the difficulties lie not only in identifying the exact origin, but also the malignant or benign character of the lesion. In the referred series, resection was performed in 13 patients who turned out to have benign disease after histopathologic examination of the specimen[13]. And this is not uncommon: A previous study of 132 resections for presumed proximal bile duct malignancy reported a 15% false positive rate[19]. Finally, most of the causes of unresectability in HCCA constitute features difficult to determine preoperatively with imaging techniques such as small peritoneal metastasis, lymph node involvement or local ingrowth. That is why HCCA assessment constitutes one of the most difficult tasks of the hepatobiliary specialized radiologists.

SL will be useful in those patients with unsuspected extended disease in whom a nonsurgical palliative procedure is of benefit, and therefore could avoid an unnecessary laparotomy. HCCA patients would therefore, at least theoretically, benefit largely from SL: there is a high rate of undetected tumoral extension and there is currently enough evidence of the benefit of the percutaneous or endoscopic placement of self expanding metal stents for palliation of unresectable cases[20]. Nevertheless, as explained below, its yield is not as high as we could expect and lower than for other hepatobiliary malignancies. But before, we will discuss about the possibility of port-site metastasis, as it was a great concern at the early beginnings of the technique. Large series of different types of oncological resection procedures have confirmed the safety of the laparoscopic approach. The rate of incisional recurrence after open surgery seems to be similar to the port-site recurrence observed. To our knowledge, there are no reported any port-site recurrence after SL in HCCA.

Regarding the evidence for the diagnostic yield of SL in HCCA, there are scarce available data, and the published series are extremely variable. Cholangiocarcinoma is a rare disease, accounting for less than 1% of all human malignancies[1]. Many clinical series, therefore, extend over a prolonged period of time, often greater than 20 years[21-23]. With regard to SL role (Table 1), one of the largest study, with 84 patients, was performed over an 11-year period[17], during which the quality of imaging undoubtedly varied[4]. Moreover, as reported by some authors[17], SL may have not been used universally, but with a selective approach, what makes it even more difficult to determine the real global diagnostic yield of this technique.

We find an additional difficulty when interpreting the results of the series. Most of the studies include different types of hepatobiliary[15,16] or pancreatobiliary[9,14,24,25] malignancies, and there are few studies fo-

cused exclusively in SL in HCCA[17,18]. This makes it difficult to extract the information specifically regarding HCCA. Nevertheless, we can get some interesting information from this apparent jumble of data. Although all of them are bile duct tumors (HCCA, GBC or distal cholangiocarcinomas), they have different patterns of spread that will affect their respective SL diagnostic yields. In this context, the worst rates are for HCCA[16]. In 2002 the MSKCC published an analysis of 100 patients with biliary cancers (44 GBC and 56 HCCA). The diagnostic yield in GBC was significantly superior than that obtained for HCCA (48% *vs* 25%)[15]. This is due to their particular spread tendency: GBC tends to spread with peritoneal and liver metastases, whereas the most common cause of unresectability in HCCA was vascular invasion and lymph node metastasis. SL easily identifies the first ones, but the second ones are often missed.

Due to the low overall efficacy to identify unresectable disease in HCCA (less than 30%), the MSKCC group proposed in 2001 performing SL only in those patients with higher risk of holding unresectable disease according to a preoperative staging system[1]. In their study, those patients with locally advanced but potentially resectable HCCA, the yield of laparoscopy was greater, 36% (12/33, T2/T3 tumors) *vs* 9% (2/23, T1 tumors)[15]. T2 and T3 patients would constitute therefore the HCCA patients that should undergo LS before surgical exploration.

The most recent available evidence in this subject is from 2011. Ruys *et al*[18] published a study of 175 patients with suspected HCCA who underwent SL during the past decade. As shown in Table 1, the overall yield of SL decreased from an average 25% of earlier reports to 14%. The authors consider this is likely the result of imaging techniques evolution and improvement during this period of time and therefore they conclude that the place of SL in the workup of patients with HCCA should be reconsidered. As this is the largest and more recent series published to date, it is worth taking a closer look at it. At final pathology, 12 patients showed benign disease, fact that also has an impact in the yield. Reviewing data of Ruys *et al*[18], LUS was only performed in four (out of 175) patients. At laparotomy, they identified several unresectable cases that-they declare-would have been spared with a more extensive SL: twenty-one patients were identified with distant positive lymph nodes precluding a curative resection and an additional 13 patients with positive lymph nodes nearby the celiac trunk or common hepatic artery would have increased the yield of SL to 20%. It is not known if this disease could have been identified if SL was performed more thoroughly by a highly experienced surgeon or with the addition of LUS. This is a very interesting study, but the facts above discussed recommend that not definitive conclusions should be drawn from this apparent drop of yield. Nevertheless, the proportion of patients that were ultimately resected raised to 51% as opposed to 27%-45% in previous studies.

With regard to the use of LUS, it seems reasonable that as it offers additional information, its use would therefore increase the yield of SL. In fact, several early reports soon showed this ability to increase the sensitivity of SL[9-11] in hepatobiliary and pancreatic cancers. In the study from Edinburgh[17], LUS increased the diagnostic efficacy from 24.3% to 41.5%. As shown in Table 1, 20 patients out of 84 were identified as having unresectable disease by LS alone. Adding LUS, a further 14 patients were deemed unresectable (one with intraparenchymal metastases and 13 due to locally advanced disease). Nevertheless, this is not a consistent finding, and it remains controversial since Tilleman *et al*[13] reported a limited value of LUS in a series of 110 patients with malignant proximal bile duct obstruction (that includes an undetermined number of patients with GBC). LUS was performed in 74 patients, 12 of whom already had histologically proved metastases detected on SL alone. Among the other 62 patients, metastasis was suspected in 11 patients and locally extensive disease in eight, but histologic proof could only be obtained in one patient. The authors consider that LUS is a waste of time, as in their experience approximately half of the time was used for the LUS imaging. They explicitly recommend diagnostic laparoscopy without LUS[13]. Other authors consider the findings of LUS difficult to interpret[24], and as previously said, some authors have abandoned its use.

A final comment about logistic aspects. There are two different subset of patients to consider. The first group of patients are those with apparent resectable disease who would need preoperative external drainage or portal vein embolization. In them, SL should be performed prior to these procedures. The early detection by SL of occult advanced disease can avoid unnecessary invasive procedures and lead to immediate institution of palliative care[16]. The second group are those patients with a potentially resectable HCCA and no need of preoperative procedures. In them, SL should be followed by laparotomy in the same session, but in some hospitals this is not always possible. As reported by Tilleman *et al*[13], in those patients who undergo a "delayed" laparotomy, the total hospital stay was longer, as they are eventually admitted a second time. As a consequence, the potential financial benefit was not as great as would be possible.

In summary, the precise role of SL and LUS in the preoperative workup of HCCA remains unclear. What seems clear is that its yield has decreased in last years and therefore there is an agreement that its universal use shouldn't be recommended anymore. There is a general consensus to perform LS only in selected patients with higher risk of holding unresectable disease (T2/T3 or Bismuth type 3/4 and patients with suspicion of metastases). It would also be recommended in patients with potentially resectable disease who would need preoperative invasive procedures. Finally, SL should be performed preceding laparotomy in one session. Further studies on the benefit of SL and LUS in this subset of HCCA patients are warranted.

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