

Staging laparoscopy in patients with hepatocellular carcinoma: is it useful?

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Abstract

Background Staging laparoscopy (SL) is not regularly performed for patients with hepatocellular carcinoma (HCC). It may change treatment strategy, preventing unnecessary open exploration. An additional advantage of SL is possible biopsy of the nontumorous liver to assess fibrosis/cirrhosis. This study aimed to determine whether SL for patients with HCC still is useful.

Methods Patients with HCC who underwent SL between January 1999 and December 2011 were analyzed. Their demographics, preoperative imaging studies, surgical findings, and histology were assessed.

Results The 56 patients (34 men and 22 women; mean age, 60 ± 14 years) in this study underwent SL for assessment of extensive disease or metastases. For two patients, SL was unsuccessful because of intraabdominal adhesions. For four patients (7.1 %), SL showed unresectability because of metastases ($n = 1$), tumor progression ($n = 1$), or severe cirrhosis in the contralateral lobe ($n = 2$). An additional five patients did not undergo laparotomy due to disease progression detected on imaging after SL. Exploratory laparotomy for the remaining 47 patients showed 6 (13 %) additional unresectable tumors due to advanced tumor ($n = 5$) or nodal metastases ($n = 1$). Consequently, the yield of SL was 7 % (95 % confidence interval (CI), 3–17 %), and the accuracy was 27 % (95 % CI,

11–52 %). A biopsy of the contralateral liver was performed for 45 patients who underwent SL, leading to changes in management for 4 patients (17 %) with cirrhosis.

Conclusions The overall yield of SL for HCC was 7 %, and the accuracy was 27 %. When accurate imaging methods are available and additional percutaneous liver biopsy is implemented as a standard procedure in the preoperative workup of patients with HCC, the benefit of SL will become even less.

Keywords Hepatocellular carcinoma · Staging laparoscopy

Hepatocellular carcinoma (HCC), the sixth most common malignancy worldwide [1, 2], varies greatly in geographic occurrence and corresponding risk profile. Chronic hepatitis B and C are predominant risk factors in the development of HCC, but the strongest correlation between underlying disease and HCC development is seen with the cirrhotic liver, in which 80 % of HCCs occur [3], making this the greatest predisposing factor (Table 1).

The Barcelona-Clinic Liver Cancer (BCLC) classification [4] generally used as the standard classification for HCC was endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [5, 6]. The AASLD has established a set of criteria for the diagnosis of HCC. The current guidelines recommend radiologic imaging, such as computed tomography (CT) and magnetic resonance (MR) imaging. When both of these imaging methods show a hypervascular lesion in the arterial phase with signs of washout during the portal or late phase, an HCC is most likely. Subsequently, this classification offers a link between the tumor stage and its treatment strategy.

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Table 1 Patient demographics

	<i>n</i> (%)
Males	34 (61)
Females	22 (39)
Mean age (years)	60 ± 14
CT	56 (100)
MRI	15 (27)
HBS with SPECT	36 (64)
Compromised liver parenchyma	
Cirrhosis	
Imaging preoperatively	15/56 (27)
SL	23/45 (51)
Unresectable	9
Liver resection	17/41 (41)
Fibrosis	
Imaging preoperatively	2/56 (4)
SL	28/45 (62)
Unresectable	7
Liver resection	19/41 (46)

CT computed tomography, MRI magnetic resonance imaging, HBS hepatobiliary scintigraphy, SPECT single-photon emission computed tomography, SL staging laparoscopy

The preferred treatment for early-stage HCC is surgical resection, liver transplantation, or percutaneous ablation with curative intent (30–40 % of cases) [7, 8], depending on the size and number of lesions and the liver function. The long-term outcome for this group of patients is good, with a 5-year survival rate of 50–70 % [3, 9].

Although radiologic imaging is a noninvasive method for the staging of malignant disease, additional staging laparoscopy (SL) still is used for a variety of malignancies including esophagogastric cancers [10], gastric cancers [11, 12], adenocarcinoma of the pancreas [13, 14], and hilar cholangiocarcinoma [15, 16]. In the case of hepatic lesions, SL could offer the additional benefit of a nontumorous liver parenchyma biopsy for assessment of fibrosis and cirrhosis.

Based on additional findings, SL may change the treatment strategy for patients with HCC and patients found to be unresectable, avoiding an unnecessary laparotomy and thereby decreasing operative morbidity, complications, and length of hospital stay [17]. Therefore, studies from the University of Hong Kong supported the use of laparoscopic staging procedures before a planned laparotomy for HCC patients [18–21].

Patients with HCC that appears to be resectable on preoperative imaging may benefit from SL for evaluation of the location, size, and number of hepatic lesions; the presence of metastases; and the assessment of cirrhosis and fibrosis. However, this procedure is not regularly used for patients with HCC, and no criteria are currently known to increase the yield of SL. Therefore, this study aimed to

assess the outcomes of SL in the management of HCC to determine whether this procedure still is useful for patients with HCC.

Methods

Study population

The study analyzed 1,156 consecutive patients with HCC who underwent SL between January 1999 and December 20. All the patients undergoing SL were believed to have resectable tumors after initial imaging. The patients' demographics, preoperative imaging studies, surgical findings, resectability, operative data, and histopathologic reports were analyzed.

The diagnosis of HCC was confirmed in accordance with the guidelines of AASLD. These guidelines state that at least one imaging method (CT, MR imaging, or ultrasonography) should show arterial enhancement with subsequent loss of contrast during the venous or portal phase of imaging ("washout sign"). This is especially true for lesions occurring in the background of hepatitis, hemochromatosis, and cirrhosis, with or without elevated serum alpha-fetoprotein levels.

The standard diagnostic workup included a multiphase CT scan, MR imaging, or dynamic ultrasound of the liver as required. The diagnosis was defined by CT scan using a four-phase (blanc, arterial, portal, and late venous phase) 2.5-mm, thin-slice, contrast-enhanced CT or multiphase MR imaging with dynamic T1 contrast sequence (arterial, portal, and late venous phase [VIBE]), T2 and diffusion weighted sequences. No official imaging criteria exist for the detection of cirrhosis and fibrosis.

A multidisciplinary team consisting of a liver surgeon, hepatologist, gastroenterologist, and (interventional) radiologist evaluated the imaging studies and came up with a proposal for the treatment of patients with HCC. In general, liver resection was not indicated for patients with extrahepatic or nodal metastases, main portal trunk or inferior vena cava invasion or thrombus, or multicentric bilobar HCC. Most patients with Child-Pugh B and all patients with Child-Pugh C were excluded from resection.

If the aforementioned criteria were met, and the patient was in overall good condition to undergo resection. The HCC lesions considered for resection included one lesion involving no more than one liver lobe without vascular involvement of the remaining liver lobes and up to three lesions smaller than 5 cm (including lesions suitable for curative radiofrequency ablation in the contralateral segments).

Preoperative assessment of future remnant liver volume and function included respectively CT volumetry and

Tc-labeled mebrofenin hepatobiliary scintigraphy (HBS) with single-photon emission computed tomography (SPECT) [22]. The volumes of the total liver (TLV), tumor (TV), and future remnant liver (FRLV) were assessed preoperatively. The percentage of FRL then was calculated according to the following formula:

$$\text{FRLV} \times 100 / (\text{TLV} - \text{TV}).$$

If the FRLV was more than 30 % in healthy liver parenchyma or more than 40 % in cirrhotic parenchyma (Child-Pugh A and B), the patient was considered eligible for surgery. Otherwise, portal vein embolization was chosen to be performed after SL. A cutoff value for an FRL function of 2.69 %/min/m² identified patients at risk for the development of postoperative liver failure [23].

Surgery

With the patient under general anesthesia, SL was performed as a separate procedure, and the patient was positioned in the supine position. A TrocDoc trocar was inserted through a semicircular, subumbilical incision for optimal visualization of the entire liver. Carbon dioxide (CO₂) pneumoperitoneum at 14 mmHg was instituted, and two additional 5-mm trocars were positioned in the right and left subcostal spaces. Both the right and left lobes of the liver were systematically examined to identify any suspicious lesions.

Additionally, distant sites were examined for metastases. Laparoscopic ultrasound also was performed for further location of hepatic lesions and for exploration of metastases. However, this imaging method was used only in the beginning of the study because it was found later to be less useful. For suspicious lesions, biopsies were taken and microscopically analyzed by the pathologist. If no metastases or other signs of unresectability were found, liver resection was planned.

Major liver resections were defined as resections of three or more Couinaud segments. Minor resections were hepatectomies of fewer than three liver segments, including wedge resections and metastectomies. Hematoxylin and eosin (H&E) sections of the resection specimens were thoroughly examined by an experienced liver pathologist for assessment of well-differentiated or poorly differentiated HCC in addition to determination of fibrosis/cirrhosis of the liver parenchyma. In case of uncertainty, slides were evaluated with immunohistochemical staining using keratin 19 for poorly differentiated HCC.

Statistical analysis

The data were analyzed using statistical software (SPSS 18.0.0; SPSS, Chicago, IL, USA). Yield was defined as the

total of avoided laparotomies divided by the total number of patients undergoing SL. Accuracy was assessed by dividing the total of avoided laparotomies by all the patients with unresectable disease. Data are presented as mean \pm standard deviation unless otherwise stated. The results were considered statistically significant when *p* was lower than 0.05.

Results

A total of 56 patients (34 men and 22 women) with a mean age of 60 \pm 14 years underwent SL. All 56 patients had undergone preoperative CT scans. An MR image of the liver was obtained for 15 patients (27 %). For 36 patients (64 %) a Tc-labeled mebrofenin HBS with SPECT was performed preoperatively to assess liver functional reserve. Based on the preoperative imaging results, cirrhosis was predicted for 15 (26.8 %) of the 56 patients and fibrosis for 2 of the patients (3.6 %). All the patients were discussed in a multidisciplinary conference and deemed potentially resectable.

Staging laparoscopy

The patients for whom surgical treatment was planned are summarized in Fig. 1. For 2 (3.6 %) of the 56 patients, SL was unsuccessful because of intraabdominal adhesions. For 4 (7.1 %) of the, SL showed unresectability because of metastases (*n* = 1), tumor progression in patients with unexpected severe cirrhosis (*n* = 1), or severe cirrhosis, particularly in the non-tumor-bearing contralateral lobe (*n* = 2).

Laparoscopic ultrasound was performed for 8 (14.3 %) of the 56 patients. For two of these patients, severe cirrhosis of the liver was confirmed by ultrasonography. This did not result in a change in treatment strategy. A biopsy of the liver parenchyma on the nontumorous lobe was performed for 45 (80.4 %) of the 56 patients during SL. Of these 45 patients, 23 (51.1 %) showed cirrhosis and 28 (62.2 %) showed fibrosis, leading to changes in management for 4 (17.4 %) of the 23 patients with cirrhosis.

One complication, urinary retention, recorded after laparoscopy was managed by transurethral catheterization and bladder training. None of the patients experience postoperative ascites as a result of SL. No in-hospital mortality was observed.

The median hospital stay for laparoscopy was 3 days (range, 2–6 days). Subsequent laparotomy was canceled for five patients because of disease progression based on imaging studies after SL. The median interval between SL and subsequent imaging was 39 days (range, 8–73 days). The median time between laparoscopy and explorative laparotomy was 37 days (range, 0–112 days; *n* = 47).

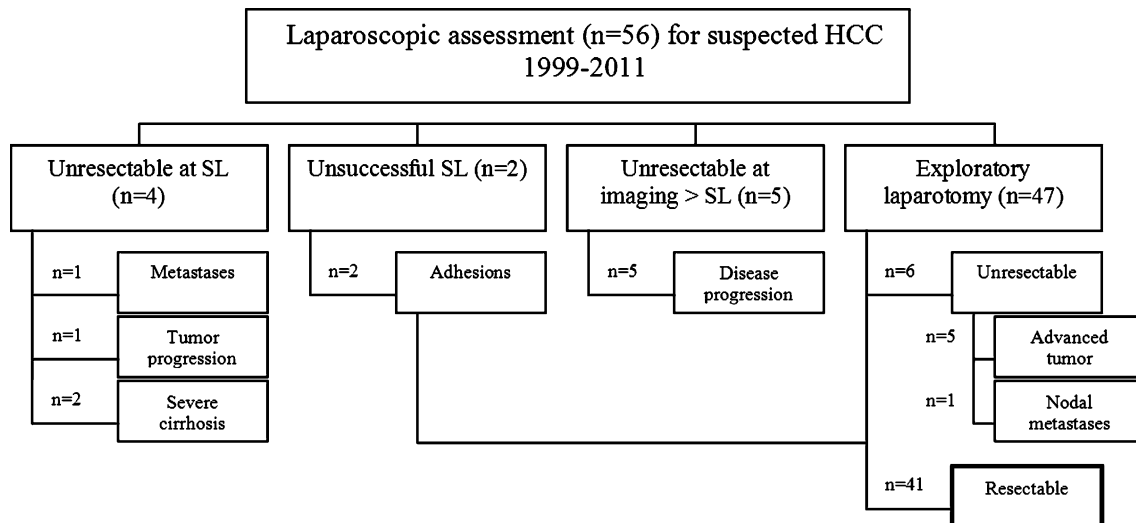


Fig. 1 Patients with hepatocellular carcinoma (HCC) treated surgically from 1999 to 2011

Laparotomy

Exploratory laparotomy for the remaining 47 patients showed resection to be impossible in an additional 6 cases (13 %, Fig. 1) due to peritoneal seeding ($n = 1$), advanced tumor ($n = 4$), or distant nodal metastases ($n = 1$). Consequently, the accuracy of SL was 27 % (4/15; 95 % confidence interval [CI], 11–52 %), and the yield was 7 % (4/56; 95 % CI, 3–17 %).

Histopathologic examination confirmed the diagnosis of HCC for all the resected patients ($n = 41$). Microscopic examination of the liver parenchyma in the resection specimens showed fibrosis ($n = 19$), steatosis ($n = 23$), cholestasis ($n = 4$), or cirrhosis ($n = 23$). The pathology outcomes for cirrhosis were in accordance with the results of biopsies during laparoscopy showing cirrhosis. Staging laparoscopy showed 23 patients with cirrhosis, leading to treatment changes for 4 patients. For the remaining 19 patients, microscopic examination of the resection specimens similarly showed cirrhosis. Cirrhosis was found in biopsies taken during laparotomy for another four patients.

Microscopic examination of the specimen after surgery showed fibrosis in 19 patients. For 16 of these patients, fibrosis was already visible in the biopsies taken during SL. Fibrosis was detected in the biopsies of three patients taken at laparotomy. Hepatitis B was shown in 5 patients, and for 11 patients a diagnosis of hepatitis C was determined.

In 10 (24 %) of 41 patients, recurrent or metastatic disease was detected after a median follow-up period of 15 months (range, 3–28 months). Five of nine patients who showed recurrence of the primary tumor presented with local recurrence, and the four remaining patients had new lesions. Two patients also showed lung or lymph node metastases. Only one patient showed lung metastases. No

recurrence of primary tumor or metastases was found in 31 (76 %) of 41 patients during the median follow-up period of 10 months (range 3–117 months).

Discussion

Because liver resection is the only curative treatment option for HCC, adequate staging and selection for putative resection are mandatory. Although preoperative staging for malignancies is readily achieved by conventional imaging studies, a considerable number of unresectable disease still are detected at laparotomy. Staging laparoscopy is used to avoid these unnecessary laparotomies.

This study examined the additional value of SL for patients with a diagnosis of HCC. The findings show that in the end, laparotomy was not indicated for 27 % (15/56) of cases and that only 7 % (4/56) of the unresectable cases were detected by SL. We therefore conclude that although SL is safe for patients with HCC, its use in clinical practice is questionable because of its low yield and poor accuracy.

The amount and quality of the available literature on staging SL in HCC are limited. Two studies reported that 40–70 % of patients with liver malignancies showed unresectable disease at laparotomy [24, 25]. In 1994, Babineau et al. [26] found that 48 % (14/29) of patients with liver malignancies were not resectable at laparoscopy due to metastases ($n = 10$) or cirrhosis ($n = 4$), including six patients with HCC. Based on these results, the authors advised that diagnostic laparoscopy should be performed before laparotomy.

The findings of Lo et al. [19, 20] a few years later were in line with this statement. These authors concluded that laparoscopy with laparoscopic ultrasonography should precede a planned exploratory laparotomy for HCC. Another study

in 2008 arrived at the same conclusion that laparoscopy and laparoscopic ultrasound can identify surgically untreatable disease and thus can select optimal treatment [18].

In contrast to these reports, we showed in the current series that SL found only 7 % of the patients to be unresectable. This rate is too low to justify routine performance of the procedure. This discrepancy with others suggests that SL is applicable only for a selected group of patients.

An explanation for the low yield in our patients may be the increased accuracy of imaging methods for detection and staging of HCC in recent years, resulting in more accurate selection of resectable disease during the diagnostic workup. As stated in the AASLD guidelines, a lesion larger than 2 cm with the typical vascular enhancement pattern on contrast-enhanced CT or MR imaging is sufficient to confirm the diagnosis of HCC. The Asian Oncology Summit statement does not have the size limitation and applies the same criteria also to smaller lesions [27]. Diagnosis therefore leans heavily on arterial enhancement, with subsequent washout of the HCC lesion during portovenous or a late phase of scanning. A major limitation lies in the smaller HCC that presents without typical enhancement given the fact that early HCC often is hypovascular [28].

New and improved imaging tools have been implemented to increase the accuracy of detection. The multiphase CT scan currently is mostly performed with a 64 instead of a 16 detector row unit, making more detailed evaluation of the lesion possible. Ultrasonography also has become more accurate in recent years, especially since the introduction of contrast-enhanced ultrasonography [29].

The most progressive innovations have been made with MR imaging. First, detection of fat, glycogen, copper, and iron content in the lesion is possible with MR imaging, which helps to discriminate between liver lesions [30]. Also small lesions (<2 cm), which might remain undetected by CT scanning, are depicted with the diffusion-weighted MR images [31, 32]. Overall, improved imaging methods have increased the accuracy of HCC detection and staging, rendering SL an inefficient, additional invasive procedure in the absence of careful patient selection.

At the onset of our study, SL was thought to have an additional value in terms of assessment of (the grade of) fibrosis and cirrhosis. In our study, imaging techniques identified only 15 patients (26.8 %) with cirrhosis and 2 patients (3.6 %) with fibrosis before laparoscopy, although at SL, 23 (51.1 %) and 28 (62.2 %) patients, respectively, showed these compromised livers.

Biopsies of the nontumorous liver parenchyma taken during SL also proved reliable because the histopathologic results were consistent with the final diagnoses made in the resection specimens performed during explorative laparotomy. However, a histologic diagnosis of parenchymal disease also may be obtained by percutaneous core biopsy of the nontumorous

liver parenchyma, which in this series was omitted because the scheduled SL would provide biopsies anyway.

In addition, a recent study with transient elastography showed promising results for noninvasive assessment of fibrosis and cirrhosis in patients with compromised livers. Hence, if the diagnostic workup includes accurate imaging methods and a preoperative percutaneous liver biopsy for histologic diagnosis of parenchymal disease is implemented in the workup, the benefit of performing SL before resection will become even less.

Our study had some limitations. First, the study contained only a small number of patients. Second, the AASLD criteria were gradually implemented in our center after 2008. Therefore, not all patients followed the same diagnostic protocol, and the diagnosis occasionally was based on one conclusive imaging method or biopsy of the tumor. Third, the median interval between SL and liver resection was 36 days (range, 0–88 days) for patients undergoing resection ($n = 41$), during which time tumors may have progressed. This delay was mostly related to intercurrent infectious complications (urinary tract infection or pneumonia) or preoperative preparation (portal vein embolization, $n = 1$).

We initially performed SL for all HPB tumors. Routine SL was abandoned first for pancreatic tumors because of decreased yield and accuracy, largely due to improved imaging techniques, especially thin-sliced, contrast-enhanced CT [33]. Next, we stopped performing routine SL in hilar cholangiocarcinoma for the same reasons [34]. Currently, we finish our evaluation of SL in HCC with the same conclusions.

This overview of studies leads us to conclude that in this era, routine SL for HPB tumors should no longer be performed. Another point to consider is that laparoscopic liver resections currently are used increasingly, also for HCC in cirrhotics [35]. Examination of the intraperitoneal cavity and the liver with laparoscopic ultrasonography then would obviously precede resection in the same session.

In conclusion, the overall yield and accuracy of SL for HCC were 7 and 27 %, respectively. When accurate imaging methods are available and additional percutaneous liver biopsy is implemented as a standard procedure in the preoperative workup of patients with HCC, the benefit of SL will become even less.

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