

# Laparoscopy and Laparoscopic Ultrasonography Avoid Exploratory Laparotomy in Patients With Hepatocellular Carcinoma

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## Objective

This prospective study evaluates the value of laparoscopy and laparoscopic ultrasonography (USG) in avoiding exploratory laparotomy in patients with hepatocellular carcinoma (HCC).

## Summary Background Data

Laparotomy and intraoperative USG is the gold standard to determine the resectability of HCC. No palliation can be offered to patients found to have unresectable disease, and the surgical exploration causes morbidity.

## Methods

From June 1994 to June 1996, 110 of 370 patients (30%) with HCC were considered candidates for possible hepatic resection. Preoperative liver function was assessed using Child-Pugh grading and indocyanine green retention test. The extent of disease was evaluated with radiologic studies, including percutaneous USG, computerized tomography scan, and hepatic angiogram. Nineteen patients were excluded from the study because of previous upper abdominal surgery ( $n = 12$ ), ruptured tumors ( $n = 4$ ), refusal by patients ( $n = 2$ ), and instrument failure ( $n = 1$ ). Laparoscopy and laparoscopic USG was performed on 91 patients immediately before a planned laparotomy aiming at hepatic resection. Laparotomy was aborted when definite evidence of unresectable disease

was found on laparoscopic examination.

## Results

The median time required for laparoscopy and laparoscopic USG was 30 minutes (range, 10 to 120 minutes). Fifteen patients had evidence of unresectable disease on laparoscopic examination. Among the remaining 76 patients who underwent laparotomy, 9 had exploration only and 67 underwent hepatic resection. Thus, exploratory laparotomy was avoided in 63% of patients with unresectable disease. The laparoscopic examination failed to confirm unresectable disease more often when the tumor was  $>10$  cm in diameter. The procedure accurately assessed the adequacy of the liver remnant and the presence of intrahepatic metastases, but it was less sensitive in determining the presence of tumor thrombi in major vascular structures and the extent of invasion of adjacent organs. When unresectable disease was detected without the need for a laparotomy, the postoperative recovery was faster, and the nonoperative treatment for the tumor could be initiated earlier.

## Conclusions

Laparoscopy with laparoscopic USG avoids unnecessary laparotomy in patients with HCC and should precede a planned laparotomy aiming at hepatic resection.

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Hepatocellular carcinoma (HCC) carries a poor prognosis, and hepatic resection offers the best chance of survival. Nonetheless, surgical resection is possible only in 9% to 40% of these patients<sup>1-6</sup> because of liver cirrhosis and

advanced stages of the disease. Selection of patients for laparotomy with the intent of curative hepatic resection involves an accurate assessment of the liver function and the extent of disease. Various special liver function studies including the bromsulphthalein test,<sup>7,8</sup> indocyanine green retention test,<sup>9,10</sup> oral glucose tolerance test, and arterial ketone body ratio<sup>11</sup> are performed to assess the global liver function. However, the final judgment as to the risk of postoperative liver failure often depends on the surgeon's

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assessment of the severity of the liver cirrhosis and the size of the liver remnant at laparotomy. Despite advances in imaging techniques, significant discrepancies between the findings of preoperative investigations and those at exploratory laparotomy are not uncommon. Depending on the patient population, extent of preoperative investigations and the criteria for resectability, up to 64% of patients with HCC, are subjected to laparotomy without hepatic resection.<sup>2,6,12-15</sup> While it is true that exploratory laparotomy and intraoperative ultrasonography (USG) remain the gold standard before the final decision to proceed to hepatic resection, no surgical palliation can be offered to those with unresectable disease. Surgical exploration to confirm unresectability not only entails unnecessary hospital expenses and substantial morbidity for the patient, but it may also delay the initiation of nonoperative treatment.

Laparoscopy with laparoscopic USG combines the power of a detailed visual assessment of the liver with that of high resolution intraoperative contact ultrasound examination. Recent studies have yielded encouraging results with this minimally invasive technique in staging of liver tumors and other gastrointestinal malignancies.<sup>16-19</sup> Therefore, we conducted a prospective study to ascertain the value of laparoscopy and laparoscopic USG performed immediately before a planned laparotomy in patients with potentially resectable HCC.

## PATIENTS AND METHODS

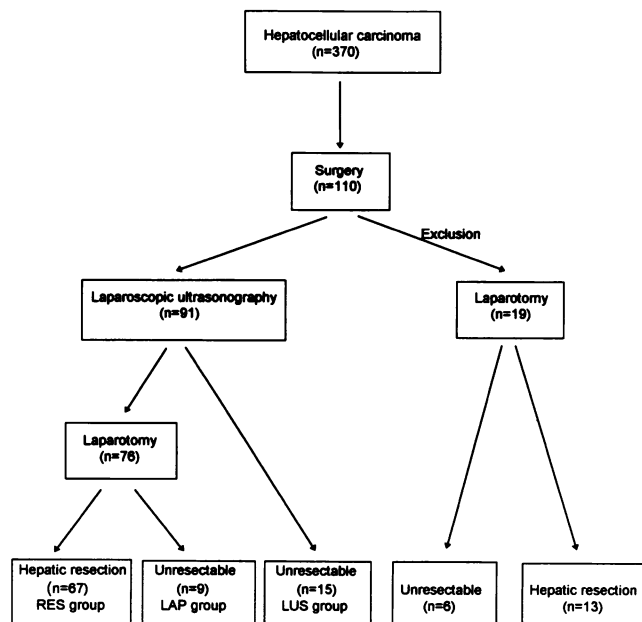
From June 1994 to June 1996, 370 patients with newly diagnosed HCC were seen in the Department of Surgery at the University of Hong Kong at Queen Mary Hospital. The possibility of hepatic resection was assessed according to a standard protocol. All patients had a chest radiograph and percutaneous USG. Laboratory blood tests including hepatitis B surface antigen, serum alpha-fetoprotein, serum albumin, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, and prothrombin time were obtained and the Pugh's modification of Child's criteria<sup>20</sup> was determined. The indocyanine green retention test was performed to assess the liver function with a maximum retention of 14% at 15 minutes as the guideline for major hepatectomy in patients with cirrhosis.<sup>9</sup> Patients with potentially resectable lesions underwent a computed tomography (CT) scan of the abdomen and a hepatic angiogram. A Lipiodol-CT scan was performed in selected patients. Further investigations, such as CT scan of the thorax, or radioisotope bone scan were performed only when there was clinical suspicion of extrahepatic metastases.

Using such criteria, 110 patients (30%) were considered candidates for possible hepatic resection and underwent surgery. Nineteen patients were excluded from this study and had an exploratory laparotomy directly to assess resectability. The reasons for exclusion were previous upper abdominal surgery (12 patients), ruptured tumors (4 patients), refusal by patients (2 patients), and instrument failure (1

patient). Laparoscopy with laparoscopic USG was attempted in 91 patients immediately before a planned laparotomy that aimed at hepatic resection. There were 77 men and 14 women who had a mean age of 53.2 years (range, 18 to 82 years). Serum hepatitis B surface antigen was positive in 82 patients (90%). Eighty-five patients were of Child-Pugh class A, 5 of class B, and 1 of class C. The mean  $\pm$ SD preoperative indocyanine green retention at 15 minutes was  $12.5\% \pm 9.1\%$ . Fifty-three patients (58.2%) had large tumors  $>5$  cm in diameter.

## Laparoscopy and Laparoscopic USG

The patient was prepared as for a planned hepatic resection and was put under general anesthesia with endotracheal intubation. A subumbilical cutdown technique was used to insert a 12-mm laparoscopic port, and pneumoperitoneum was established with carbon dioxide insufflation to a maximum pressure of 12 mmHg. Using a 30° laparoscope, the peritoneal cavity and surface of the liver was inspected. Under direct visual guidance, a second 12-mm port was inserted in the right lower quadrant at the mid-clavicular line. The laparoscopic ultrasound probe was inserted through this port and was placed in contact with the liver under the guidance of the laparoscope. In the early part of the study, a rigid 7.5 M-Hz linear array probe (Aloka UST-5526-7.5, Tokyo, Japan) was used in conjunction with a portable ultrasound monitor (Aloka SSD-500). These were subsequently replaced by another ultrasound monitor (Aloka SSD-2000) and a flexible 7.5 M-Hz probe (Aloka UST-5536-7.5), which could be steered upward and downward for better contact with the surface of the liver. Systemic examination of the liver was performed by slowly moving and rotating the probe over the entire liver. Laparoscopic inspection of the undersurface of the left lobe was completed by using the laparoscopic ultrasound probe to displace the liver. The examination was repeated after the sites of insertion for the laparoscope and laparoscopic ultrasound probe were interchanged. A guided biopsy with frozen section was performed to examine suspicious lesions that would preclude curative resection if found positive. However, for fear of dissemination, a biopsy for potentially resectable tumors was not performed. The decision for unresectability was based on the finding of disease not amenable to curative resection or an inadequate liver remnant, using the same criteria as at laparotomy and intraoperative USG. When definite evidence of unresectable disease was manifest on laparoscopic examination, laparotomy was not performed. Otherwise, if unresectability was not obvious or only was suspected but not confirmed, open exploration and intraoperative USG using a 7.5 M-Hz T-shaped probe was performed immediately. A further biopsy with frozen section was done for suspicious lesions. When resectability was determined, hepatic resection was carried out using the technique previously described.<sup>5</sup> All procedures, including laparoscopy, laparoscopic USG, intraoper-



**Figure 1.** Study design and results of laparoscopic ultrasonography.

ative USG, and hepatic resection were undertaken by the same surgical team. All the surgeons have had extensive experience in laparoscopic surgery and intraoperative USG.

## Statistical Analysis

Continuous variables were expressed as median (range) and compared using the Mann-Whitney U test. Categorical variables were compared using either the chi-square test or the Fisher's Exact test, where appropriate. Statistical analysis was performed with the help of SPSSPC+ (SPSS, Chicago, Illinois) and a  $p$  value  $< 0.05$  was taken as statistically significant.

## RESULTS

Laparoscopy with laparoscopic USG was successfully performed in all 91 patients. The median time for the procedure was 30 minutes (range, 10 to 120 minutes). The examination demonstrated definite features of unresectable disease and thus laparotomy in 15 patients (LUS group) was avoided. The remaining 76 patients underwent laparotomy. Sixty-seven patients had hepatic resection (RES group) while 9 patients were unresectable on exploration (LAP group). Thus, the use of laparoscopy and laparoscopic USG avoided exploratory laparotomy in 15 of 24 patients (63%) with unresectable disease, which increased the resectability rate at laparotomy from 74% to 88%. During the same period, 19 patients who were excluded from this study had laparotomy without laparoscopy and laparoscopic USG. Six patients had exploration only without hepatic resection, giving a resectability rate of 68% (Figure 1).

## Duration of Procedure

The median time required for completion of laparoscopy and laparoscopic USG was 45 minutes (range, 30 to 120 minutes) for the LUS group, 20 minutes (range, 15 to 35 minutes) for the LAP group, and 25 minutes (range, 10 to 90 minutes) for the RES group ( $p < 0.001$ , LUS group vs. LAP group or RES group). The significantly longer time required in the LUS group was related to the need for laparoscopic or laparoscopic ultrasonographically guided biopsy to confirm unresectable disease without performing a laparotomy.

## Demographic Data, Liver Function, and Tumor Size

The demographic data of (Table 1) the three groups of patients were comparable, and there was no difference in the preoperative liver function with reference to Child-Pugh grading or indocyanine green retention test. However, patients who underwent hepatic resection had significantly smaller tumors than those with unresectable disease ( $p < 0.05$ , RES group vs LUS group;  $p < 0.001$ , RES group vs LAP group). Patients with unresectable disease not detected by the laparoscopic examination, but found only at laparotomy, tended to have a larger tumor size than those identified by laparoscopy and laparoscopic USG ( $p = 0.06$ ). The laparoscopic examination failed to confirm unresectable disease in 7 of 12 patients with tumors  $>10$  cm and in only 2 of 12 patients with tumors  $\leq 10$  cm.

## Major Findings of Unresectability

The major findings that precluded hepatic resection in 24 patients of LUS and LAP groups are shown in Table 2. On laparoscopic examination alone, 8 of the 24 patients had evidence of unresectable disease including an inadequate liver remnant (6 patients), visible bilobar disease (5 patients) and peritoneal metastasis (1 patient). After laparoscopic USG, another 7 patients had additional features negating hepatic resection. These included bilobar intrahepatic metastases (6 patients) and tumor infiltration of main portal vein or inferior vena cava (3 patients). The remaining nine patients of the LAP group required exploratory laparotomy to detect (five patients) or to confirm unresectable disease (four patients). Thus, laparoscopy and laparoscopic USG was able to detect 6 of 7 patients with inadequate liver remnant, 11 of 13 patients with bilobar intrahepatic metastases, and the 1 patient with peritoneal metastasis. However, the procedure failed to confirm the presence of main portal vein tumor thrombi in three of five patients, inferior vena cava tumor thrombi in one of two patients, and invasion of adjacent organs in all three patients.

## Postoperative Course

There was no complication related to the laparoscopic examination itself. Two of nine patients in whom unresect-

**Table 1. DEMOGRAPHIC DATA, LIVER FUNCTION, AND TUMOR SIZE OF 91 PATIENTS WITH HEPATOCELLULAR CARCINOMA UNDERGOING LAPAROSCOPY AND LAPAROSCOPY ULTRASONOGRAPHY**

	LUS Group (n = 15)	LAP Group (n = 9)	RES Group (n = 67)
Sex (M:F)	12:3	8:1	57:10
Age (yr)*	51 (32–77)	53 (45–72)	52 (18–82)
Child-Pugh grading			
A	14	7	64
B	0	2	3
C	1	0	0
ICG retention at 15 min (%)*	11 (3.8–26.9)	14 (5–33.5)	10.5 (1.6–66.9)
Tumor size (cm)*	8 (2.5–15)	11.6 (5.2–15)†	5.8 (1.5–15.2)
>10	5	7	11
5.1–10	5	2	23
2.1–5	5	0	27
≤2	0	0	6

LUS group = unresectable disease detected by laparoscopic examination; LAP group = unresectable disease detected by laparotomy; RES group = resectable disease; ICG = Indocyanine green.

\* Median (range).

†  $p < 0.001$  LAP group vs. RES group;  $p = 0.06$  LAP group vs. LUS group.

able disease was discovered at exploratory laparotomy developed postoperative complications: one developed pneumonia and another had pleural effusion which required tapping. There was no complication in patients who underwent laparoscopy and laparoscopic USG alone. Patients of the LUS group were able to resume their diet earlier (0 day vs. 1.5 days;  $p < 0.05$ ) and also had a shorter hospital stay (5 days vs. 9 days;  $p < 0.005$ ) when compared with those of the LAP group (Table 3).

Eight patients of the LUS group and five of the LAP group subsequently received transarterial chemoembolization. Two patients of each group were treated with oral

tamoxifen and one of the LUS group received ultrasound-guided intralesional alcohol injection. The remaining four patients of the LUS group and two of the LAP group had symptomatic treatment only. The time from surgery to the performance of nonoperative treatment was less in the LUS group (11 patients) than in the LAP group (7 patients) (6 days vs. 23 days;  $p < 0.05$ ). The median survival, however, was not significantly different (Table 3). For the 67 patients who underwent hepatic resection, the 1-year survival rate was 76%, and there was no evidence of metastasis at the laparoscopic port-sites or laparotomy wounds in any patient at a median follow-up of 10 months (range, 1 to 30 months).

**Table 2. MAJOR FINDINGS PRECLUDING HEPATIC RESECTION IN 24 PATIENTS WITH HEPATOCELLULAR CARCINOMA**

	LUP Group (n = 15)	LAP Group (n = 9)
Inadequate liver remnant/severe cirrhosis	6	1 (1)
Peritoneal metastasis	1	0
Bilobar intrahepatic metastasis	11	2 (1)
Main portal vein tumor thrombus	2	3 (2)
Inferior vena cava tumor thrombus	1	1
Invasion of adjacent organs	0	3*

Some patients had more than one feature precluding hepatic resection. Values in parentheses are number of patients with findings suspected on laparoscopic examination.

LUS group = findings at laparoscopy and laparoscopic ultrasonography; LAP group = findings at laparotomy.

\* Invasion of colon and duodenum in one patient and invasion of the diaphragm close to the inferior vena cava in two patients.

## DISCUSSION

Despite recent advances in hepatic resection techniques, surgical resection for HCC should be offered only to se-

**Table 3. POSTOPERATIVE COURSE OF 24 PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA**

	LUS Group (n = 15)	LAP Group (n = 9)
Tolerate normal diet (days)*	0 (0–2)	1.5 (0–4)†
Postoperative complications	0	2
Hospital stay (days)*	5 (0–16)	9 (4–31)‡
Time from surgery to nonoperative treatment (days)*	6 (0–79)	23 (2–91)†
Median survival (mo)	5	5.7

\* Median (range).

†  $p < 0.05$ .

‡  $p < 0.005$ .

lected patients with sufficient liver function and unilateral disease amenable to curative treatment.<sup>21</sup> Hepatectomy in the presence of poor hepatic reserve will often result in postoperative liver failure which carries a greater mortality rate.<sup>22</sup> Likewise, palliative resection for patients with bilobar or metastatic disease offers no meaningful survival advantage.<sup>13,23</sup> The ultimate goal of various modalities of preoperative assessment is the selection of the appropriate candidates suitable for hepatic resection. Nonetheless, with the use of preoperative indocyanine green retention test, percutaneous USG, contrast-enhanced CT scan, and hepatic angiography, more than 25% of our patients subjected to surgery were on exploration not resectable. Because the survival time of these patients with unresectable disease is limited, an exploratory laparotomy would entail significant suffering and morbidity. Thus, an accurate but less invasive technique for determining resectability is needed.

Diagnostic laparoscopy, as a staging technique for hepatic malignancy, is sensitive in identifying underlying liver cirrhosis, peritoneal metastasis, and satellite lesions on the surface of the liver. Babineau et al.<sup>24</sup> reported that 14 of 29 patients with hepatic malignancies had laparoscopy evidence of unresectable disease. Most of their patients suffered from metastatic liver cancer, and peritoneal seedlings were the most common laparoscopic finding that precluded hepatic resection. Autopsy studies, however, showed that HCC had a much lower incidence of peritoneal metastases than other hepatic malignancies.<sup>4</sup> In a clinical series of 48 patients who were subjected to surgery for HCC,<sup>6</sup> only 1 of the 14 patients who was not resectable had peritoneal metastasis. In the present series, concomitant liver cirrhosis with inadequate liver remnant, bilobar intrahepatic metastases, and tumor thrombi in major vascular structures were the three most common findings that precluded hepatic resection in patients with HCC. Intrahepatic metastasis and tumor thrombus are often not visible or palpable and can readily be detected by intraoperative USG only.<sup>25</sup> Thus, the value of diagnostic laparoscopy alone was limited in patients with HCC and the procedure could detect only 8 of 24 patients with unresectable disease in this series.

Recent advances in minimal access surgery has promoted the development of laparoscopic ultrasonographic transducers. Laparoscopy with laparoscopic USG combines the less invasive advantage of minimal access surgery with the greater accuracy of intraoperative contact USG. The sensitivity of laparoscopic USG in detecting intrahepatic lesions was comparable to that of open contact USG in a bench top model of hepatic metastases.<sup>26</sup> The clinical use of laparoscopy and laparoscopic USG in staging liver tumors was recently reported. Timothy et al.<sup>16</sup> described their experience of the technique in a heterogeneous group of patients with different types of liver tumors, including benign lesions. In some cases, however, the purpose of the procedure was diagnostic rather than staging, and the laparoscopic examination was not always performed after full preoperative radiologic assessment had been completed. In a retro-

spective study of 13 patients with liver metastases,<sup>17</sup> the accuracy of laparoscopic USG was compared with that of CT portography. Laparoscopy and laparoscopic USG share the objectives of other modalities of preoperative assessment in selecting the appropriate candidates for hepatic resection. However, the procedure itself is an operation under general anesthesia and is invasive when compared with other radiologic investigations. Hence, we tend to reserve this procedure only for those patients with potentially resectable HCC after less invasive investigations had been completed. To ascertain whether this minimally invasive technique can replace open exploration for determination of resectability, its accuracy should be compared with intraoperative USG at laparotomy.

Our data show that laparoscopy with laparoscopic USG is highly accurate in assessing the adequacy of the liver remnant and the presence of intrahepatic metastases. However, the procedure is less accurate than laparotomy and intraoperative USG in determining the presence of tumor thrombi in major vascular structures and the extent of invasion of adjacent organs. When compared with intraoperative USG at laparotomy, the definite limitations of the laparoscopic technique are: 1) palpation of a lesion is not possible under the laparoscope; 2) when direct invasion of adjacent organs is suspected, a trial of dissection cannot be performed; 3) the angle and direction of ultrasound scanning under the laparoscope is limited by the position of the laparoscopic ports; and 4) preliminary mobilization and manipulation of the liver to improve the angle of scanning cannot be performed. Such limitations are most obvious in patients with large tumors and account for the lower accuracy of the laparoscopic examination in determining resectability when the tumors are >10 cm in diameter. Thus, bulky tumors interfere with the angle and direction of the laparoscopic ultrasound probe and limit the adequacy of scanning. In addition, invasion of adjacent organs tends to occur more often with these large tumors. To assess whether the tumor is adherent to or infiltrating the colon or the duodenum, a careful trial of dissection is necessary. Similarly, invasion of the diaphragm can only be detected after mobilization of the liver's right lobe. Such a trial of dissection for a large tumor is potentially dangerous under the laparoscope and only should be attempted at laparotomy.

With the use of laparoscopy with laparoscopic USG, we were able to avoid exploratory laparotomy in more than 60% of our patients with unresectable disease. By successfully avoiding the need for open exploration in these 15 patients, the morbidity rate was reduced, the hospital stay was shortened, and nonoperative treatments could be started earlier. For the 76 patients who subsequently underwent laparotomy and did not benefit from the laparoscopic examination, although the procedure caused an extra operating time of 20 to 25 minutes, there was no procedure-related complication. The report of port-site metastases after laparoscopic surgery in patients with occult malignancy<sup>27</sup> raises concerns about this important complication after diagnostic

laparoscopy. The incidence was 1.6% in a retrospective study of 250 patients who underwent staging laparoscopy for gastrointestinal malignancy.<sup>28</sup> To avoid tumor seedling, biopsy should be performed only for unresectable tumors or for suspicious metastases that would preclude curative resection. Biopsy should be avoided in patients with potentially resectable disease. In this series, no laparoscopic port-site or laparotomy wound metastasis developed in patients who underwent hepatic resection with curative intent, and the laparoscopic examination did not seem to jeopardize the outcome of these patients.

In conclusion, laparoscopy with laparoscopic USG avoids the morbidity associated with exploratory laparotomy in patients with HCC. Although the technique may be less accurate for tumors >10 cm in diameter, we would recommend that the procedure should be performed in all cases before a planned laparotomy aiming at hepatic resection.

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