Consensus Statement

The Asia Pacific Consensus Statement on Laparoscopic Liver Resection for Hepatocellular Carcinoma: A Report from the 7th Asia-Pacific Primary Liver Cancer Expert Meeting Held in Hong Kong

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Keywords

3D laparoscopy · Cirrhosis · Evidence · Hepatocellular carcinoma · International consensus conference · International consensus guidelines · Hepatectomy · Liver resection

Abstract

Background: Laparoscopic liver resection has been gaining momentum, and it has become an accepted practice after the two international consensus conferences where experts worked up guidelines to standardize this approach and improve its safety. However, most laparoscopic hepatectomies were performed in patients with liver metastases. The concurrent presence of liver cirrhosis with hepatocellular carcinoma (HCC) poses a great challenge to clinicians trying to establish a routine use of laparoscopic liver resection for HCC. **Summary:** The first Asia Pacific consensus meeting on laparoscopic liver resection for HCC was held in July 2016 in Hong Kong. A group of expert liver surgeons with experience in both open and laparoscopic hepatectomy for HCC convened to formulate recommendations on the role and perspective of laparoscopic liver resection for primary liver cancer. The recommendations con-

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solidate the most recent evidence pertaining to laparoscopic hepatectomy together with the latest thinking of practicing clinicians involved in laparoscopic hepatectomy, and give detailed guidance on how to deploy the treatment effectively for patients in need. **Key Message:** The panel of experts gathered evidence and produced recommendations providing guidance on the safe practice of laparoscopic hepatectomy for patients with HCC and cirrhosis. The inherent advantage of the laparoscopic approach may result in less blood loss if the procedure is performed in experienced centers. The laparoscopic approach to minor hepatectomy, particularly left lateral sectionectomy, is a preferred practice for HCC at experienced centers. Laparoscopic major liver resection for HCC remains a technically challenging operation, and it should be carried out in centers of excellence. There is emerging evidence that laparoscopic liver resection produces a better oncological outcome for HCC when compared with radiofrequency ablation, particularly when the lesions are peripherally located. Augmented features in laparoscopic liver resection, including indocyanine green fluorescence, 3D laparoscopy, and robot, will become important tools of surgical treatment in the near future. A combination of all of these features will enhance the experience of the surgeons, which may translate into better surgical outcomes. This is the first consensus workforce on laparoscopic liver resection for HCC, which is a unique condition that occurs in the Asia Pacific region.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide [1]. It has a very high prevalence in the Asia Pacific region because of the high prevalence of chronic hepatitis B and C, and it is one of the top cancer killers in the region. Unfortunately, patients with HCC usually present with underlying liver cirrhosis, which is a major adverse factor for liver resection [2–4].

Laparoscopic liver resection is becoming an accepted approach for liver cancers [5, 6], particularly on liver metastases [7–11], after two international consensus conferences held in Louisville in 2008 [12] and Morioka in 2014 [13]. To date, there has been no randomized controlled trial published. However, the number of cases published has been rapidly increasing to more than 9,000. Many of these cases were reported in the form of case series [14–17], case control study [18–28], or systematic review and meta-analysis [5, 6, 29–32]. Many specialized centers of liver cancer management are now entering the exploration and assessment phase. In HCC patients with underlying liver cirrhosis, laparoscopic liver resection is difficult because of the presence of portal hypertension and thus a high bleeding tendency which renders parenchymal transection difficult [15, 28, 33]. Safe performance of the operation calls for ample experience [34–36].

The first Asia Pacific consensus meeting for HCC was held in conjunction with the 7th Asia-Pacific Primary Liver Cancer Expert Meeting in Hong Kong in order to achieve the goals of defining the role of laparoscopic liver resection in HCC management and developing recommendations and guidelines.

The organizing committee formulated 10 questions to collect evidence on issues on benefits and techniques of laparoscopic liver resection for HCC (Table 1).

In a series of meetings held on 8–10 July, 2016, a group of expert liver surgeons with experience in both open and laparoscopic hepatectomy for HCC convened to formulate recommendations on the role and perspective of laparoscopic liver resection for primary liver cancer.

A search of the literature in English was performed through MEDLINE, Embase, and Cochrane Library for articles on laparoscopic liver resection published in the period from

Table 1. Session topics on laparoscopic resection for primary liver cancer

- 1 Evidence on laparoscopic liver resection for HCC
- 2 Laparoscopic liver resection for small HCCs: radiofrequency ablation vs. laparoscopic hepatectomy
- 3 Laparoscopic liver resection in patients with marginal liver function
- 4 Laparoscopic liver resection in patients with portal vein involvement
- 5 Laparoscopic liver resection learning curve issues
- 6 Robotic liver resection for HCC
- 7 The use of augmented techniques for laparoscopic hepatectomy (indocyanine green fluorescence and 3D systems)
- 8 The use of hemostatic agents in patients with cirrhosis
- 9 Laparoscopic approach to treating HCC in difficult locations

1991 to July 2016. Consensus statements were developed by group members designated before the meetings. The statements were circulated among the members and modified according to feedback. At the meeting, each statement was assessed on a five-point Likert Scale (1 – Accept completely, 2 – Accept with some reservations, 3 – Accept with major revisions, 4 – Reject with reservations, 5 – Reject completely). Votes on the statements were recorded instantly by a secretary of the meeting. Agreement by 80% of the group to accept completely a statement was defined as consensus on that statement. A statement on which consensus was not achieved was modified and put to the vote again until consensus was reached. Finally, the group evaluated each statement's level of evidence as per the 2011 Oxford criteria [37]. In the following, each statement's level of evidence is shown.

Consensus Recommendations

Evidence on Laparoscopic Liver Resection for HCC

- 1 Laparoscopic minor liver resection for early stage ($\leq T2$) HCC located in segment 2, 3, 4b, 5, or 6 is a safe option in centers with experience. [Level 3 evidence]
- 2 Laparoscopic minor liver resection in difficult locations (1, 4a, 7, 8 (difficulty score intermediate grade or above)) should be performed in centers of excellence. [Level 3 evidence]
- 3 Laparoscopic major hepatectomy (more than 3 segments) is an operation with high complexity and should be carried out in centers of excellence. Further evidence will support the development of this practice. [Level 3 evidence]

The Panel has discussed the definition of center of excellence for laparoscopic liver resection in order to ensure good practice and patient safety. A center of excellence for laparoscopic liver resection should consist of a dedicated multidisciplinary liver team that includes surgeons, hepatologists, radiologists, oncologists, anesthesiologists, and nurses to ensure every patient receives the best treatment option for his/her condition. The center performs at least 30 laparoscopic liver resections per year. Surgeons must have performed at least 100 laparoscopic liver resections on their own over a lifetime, and at least 20 cases per year.

There is more evidence on the short- and long-term results of laparoscopic minor liver resection for HCC [18, 28, 38–45]. It has been consistently observed that the laparoscopic approach to minor liver resection is associated with less blood loss [26, 45–48], less blood transfusion [26], and shorter hospital stay [22, 25, 26, 46, 48]. It has been proven that the long-term results of this treatment modality are not inferior to those of the open approach [5, 24, 46, 48, 49]. One recent study showed that laparoscopic minor hepatectomy was associated with a better survival outcome [28]. In the long run, the benefits of the no-touch tech-

nique, less blood loss, and less transfusion could be reflected by better overall and disease-free survival.

On the other hand, the evidence for laparoscopic major hepatectomy for HCC is less strong as this surgery remains a technically challenging procedure, particularly in patients with liver cirrhosis [50]. Worldwide, the number of surgeons who can perform this procedure proficiently is relatively small, when compared with open liver resection [51]. More evidence is needed to support the growth of laparoscopic major liver resection for HCC patients.

Patient Selection for Laparoscopic Hepatectomy for HCC

Liver Function Evaluation

- 4 Selection of patients for laparoscopic liver resection for HCC in terms of liver function should be the same as in open liver resection. [Level 3 evidence]
- 5 Laparoscopic liver resection for HCC is reported to be better tolerated in patients with marginal liver function. [Level 3 evidence]

Selection of HCC patients for laparoscopic liver resection should largely follow the safety principles used in open hepatectomy [4, 52]. In many studies, HCC patients were considered suitable for laparoscopic hepatectomy if they could tolerate general anesthesia, had Child A liver function, and had a suitable platelet count ($>40 \times 10^9/L$ for minor hepatectomy, $>80 \times 10^9/L$ for major hepatectomy) [46, 53, 54]. Patients were not considered suitable if they had decompensated Child B or Child C liver cirrhosis [52]. In Asia, preoperative indocyanine green retention rate at 15 min after injection is given emphasis [55, 56]. Studies have shown that some patients with Child A cirrhosis may not tolerate hepatectomy well, while some patients with Child B liver cirrhosis can perform well after liver resection [53, 57, 58]. The acceptable indocyanine green retention rates for major hepatectomy range from 14.4 to 20%, depending on the experience of individual centers [59–65].

Tumor Size Consideration

- 6 Laparoscopic liver resection for HCCs ≤ 5 cm in favorable locations is a safe procedure in centers with experience. [Level 3 evidence]
- 7 Laparoscopic liver resection for HCCs >5 cm should only be carried out in centers of excellence. [Level 4 evidence]
- 8 Laparoscopic liver resection is not usually indicated for HCCs >10 cm. Patients should be carefully selected, and the resection should be performed only in centers of excellence. [Level 4 evidence]

In most of the reviews in the literature, the median tumor size was smaller than 5 cm in laparoscopic liver resection for HCC [66, 67]. Most surgeons performing laparoscopic liver resection follow the rules recommended by the Louisville statement 2008. According to the statement, the most favorable indication for laparoscopic resection is a solitary lesion, 5 cm or smaller, located in one of the peripheral liver segments 2–6 [12]. The panel considered that laparoscopic resection of tumors larger than 5 cm are only possible in centers of excellence because these lesions will raise concerns about oncological compromise, margin clearance, and risk of rupture during manipulation [12, 66, 68]. Likewise, for tumors measuring about 10 cm, there will be the consideration of specimen delivery – a considerably bigger wound will need to be made. However, the panel also took into consideration the fact that experience and proficiency in laparoscopic liver resection for HCC are growing, and many centers have successfully performed laparoscopic liver resection in more difficult locations [69] and on bigger tumors [70–72], and thus suggested that laparoscopic resection for these difficult cases should only be performed in centers of excellence with careful patient selection.

Tumor Location, Anatomical Resection versus Nonanatomical Resection

9 Laparoscopic wedge liver resection for small (<2 cm) peripheral HCCs is the preferable surgical option. [Level 3 evidence]

10 Laparoscopic anatomical liver resection (including monosegmentectomy and subsegmentectomy) is generally recommended for patients with HCC. [Level 3 evidence]

Anatomical resection has always been advocated by many surgeons in the hope of producing better oncological outcomes [73–76] (reference included).

On the other hand, in the management of HCC with liver cirrhosis, liver preservation is an important concept in preventing posthepatectomy liver failure. Anatomical monosegmentectomy seems to be a good option to achieve maximal oncological clearance and liver function preservation. However, anatomical liver resection requires more complex surgical skills [77]. The transection plane usually lies along vital and vulnerable anatomical structures such as the portal vein, hepatic veins, and bile ducts. Anatomical monosegmentectomy in laparoscopic surgery is highly complex and should only be performed by surgeons at centers of excellence. Many factors affect the recurrence of HCC, including tumor size, presence of microvascular invasion, Edmondson grading of the cancer cells, and width of surgical resection margin [78–80]. Anatomical resection cannot alter these factors and should be performed only when it is technically feasible and when the function of the remnant liver would allow. As it is usually more complicated than a wedge resection, an anatomical resection is likely to have a higher difficulty grade, a longer operation time, more blood loss, and a higher complication rate, especially if the tumor is located at the periphery of the liver. A smart clinical decision has to be made in the field.

The Role of Laparoscopic Liver Resection versus Radiofrequency Ablation

11 The effectiveness of laparoscopic liver resection is comparable to that of radiofrequency ablation, with a lower recurrence rate in patients with small HCCs. [Level 3 evidence]

12 Laparoscopic liver resection minimizes the risk of local intrahepatic recurrence, which can result from preexisting microscopic tumor foci or tumor dissemination by radiofrequency ablation. [Level 3 evidence]

13 Laparoscopic liver resection is favored in patients with peripheral HCCs in segments 2–6, and/or when a histological assessment is desirable. [Level 4 evidence]

Some case-control series showed that laparoscopic liver resection of smaller HCCs had favorable midterm outcomes [28, 81]. In studies comparing open liver resection with radiofrequency ablation in treating tumors smaller than 2 cm, the two modalities resulted in similar overall survival [82–85], but disease-free survival after open liver resection was better [81, 85–87]. Theoretically, hepatectomy removes all tumor cells from the liver and reduces the chance of intrahepatic recurrence from the same tumor. For tumors larger than 3 cm, liver resection was shown to produce better overall survival [88]. The advantages of radiofrequency ablation over open liver resection include less invasiveness, shorter operation time, less blood loss, and faster recovery [87]. Laparoscopic liver resection has all these advantages and also better oncological clearance [28, 89]. In actual practice, radiofrequency ablation can still be an easier option if the HCC is small and in a difficult location.

HCC with Portal Vein Invasion

The panel has discussed the issue of laparoscopic liver resection with portal vein invasion. However, as the evidence on this area is still limited, we did not conclude to make a recommendation.

HCC with portal vein invasion is associated with poorer prognosis [90–92]. Liver resection provides better survival when compared with nonsurgical treatments such as transarterial chemoembolization and targeted therapy [93, 94]. Most of the evidence arose in studies of

open liver resection. The feasibility of laparoscopic liver resection for HCC with portal vein resection has been reported [95], but long-term results are still lacking. The panel agreed that laparoscopic liver resection for HCC with portal vein invasion is feasible if the tumor thrombus involves only the left lateral section branches. In selected centers, laparoscopic hepatectomy with portal vein reconstruction is possible if the tumor involves only Vp3 and Vp4. Favorable long-term outcomes are needed to validate this type of procedure.

Learning Curve of Laparoscopic Liver Resection for HCC

- 14 The difficulty scoring system is useful for evaluation of the operation difficulty of laparoscopic liver resection for HCC. [Level 3 evidence]
- 15 Laparoscopic liver resection for HCC classified into high and intermediate difficulty should be performed in centers of excellence. [Level 4 evidence]
- 16 It is necessary to gradually improve skills according to the difficulty level. [Level 4 evidence]

The safety and continuity of laparoscopic liver resection can only be ensured by learning and education. A difficulty score system was proposed in the Morioka consensus meeting in 2014, which categorized laparoscopic liver resection into three levels: easy, intermediate, and expert [13, 96]. Factors affecting the difficulty include tumor location, tumor size, presence of cirrhosis, and proximity to major vessels. This grading system has been validated by several centers [97–99]. It is generally agreed that the system provides a good reflection of the complexity of the surgery. The difficulty scale gives a good guideline on how to learn laparoscopic liver resection. It helps to prevent mismatch of experience and complexity, which is a main reason for surgical misfortune.

Gradual improvement of skill comes in accumulating experience by climbing up the difficulty scale ladder [35, 36, 51].

The Use of Augmented Laparoscopic Technology, Robots, and Other Adjuncts in Hepatectomy

Indocyanine Green Fluorescence and 3D Laparoscopy

- 17 Indocyanine green fluorescence is a promising technology that may have a value on laparoscopic liver resection for HCC. [Level 4 evidence]
- 18 3D laparoscopy is a useful adjunct that may enhance surgeons' performance in laparoscopic liver resection for HCC. [Level 4 evidence]

Technological advancement is an irreversible evolution that allows progression of surgical procedures. The use of high-definition video cameras and display units is a major breakthrough in laparoscopic surgery. Amplification of the visual field makes meticulous dissection possible [100, 101]. In recent years, the development of the 3D laparoscopic system has become very mature. Studies have shown that surgeons perform better in a 3D laparoscopic environment where better spatial recognition is observed [102]. It improves hand-eye coordination. As a result, complex laparoscopic work like suturing takes less time [101]. Laparoscopic liver resection can also be helped by the use of indocyanine green fluorescence, which has the advantages of real time illumination of occult lesions [103, 104], revealing the surgical margins [105], identifying anatomical landmarks of the liver [106–110], and showing a more precise pathology in surgical specimens [111, 112]. These are relatively new technologies, and it may be difficult to demonstrate a statistically significant clinical difference with their use. Nonetheless, these technologies are becoming common practice, and as the prices of these units are going down, they will become standard equipment very soon.

Robotic-Assisted Hepatectomy

- 19 The feasibility and safety of robotic minor/major resection for HCC have been demonstrated with trained surgeons and appropriate patient selection. [Level 3 evidence]
- 20 The robotic approach may have a role in treating HCC in difficult segments and bring about a higher rate of major hepatectomy in some centers. [Level 3 evidence]
- 21 Comparative studies have not shown any significant differences in the short-term outcomes brought by the laparoscopic approach [Level 3 evidence] and evidence is needed to define its long-term oncological outcomes for HCC

The use of robots has become another main stream in laparoscopic surgery. Hospitals with robotic surgical facilities have made good use of them and favorable outcomes have been observed. Studies have shown that pure laparoscopic hepatectomy and robotic surgery have comparable outcomes [113–117]. The learning curve of robotic surgery may be shorter, but the ease of entry may be more restricted since the equipment is not widely available. The panel agreed that robotic surgery may enhance the feasibility of the laparoscopic approach for HCC.

The Use of Hemostatic Agents

- 22 Further evidence is required to support the use of hemostatic agents for laparoscopic liver resection for HCC with cirrhosis. [Level 4 evidence]

The use of hemostatic agents after completion of liver transection is a common practice in laparoscopic liver resection. This may give the operating surgeons an additional sense of security, particularly if the liver is cirrhotic [118, 119]. The panel agreed that so far there is inadequate evidence that the use of hemostatic agents will prevent secondary bleeding after laparoscopic liver resection for HCC. There is very little such evidence in open liver resection either [120–122]. The key to prevent re-bleeding is adequate hemostasis during laparoscopy. During liver transection, the central venous pressure is maintained at a low level (<5 mm Hg), if possible, by strict control of intravenous fluid administration to reduce venous bleeding from the liver. The patient should also be placed in the reversed Trendelenburg position around 15–30°. An additional tip is to check the final hemostasis at a reduced pneumoperitoneal pressure and an adequate systolic blood pressure before wound closure.

Summary

In this consensus meeting, the expert panel made 22 recommendations on the position of laparoscopic hepatectomy for HCC. These recommendations consolidate the latest evidence pertaining to HCC treatment and provide detailed guidelines on how to deploy laparoscopic liver resection effectively for this group of patients. Although the panel had performed an extensive review on this topic, most of the evidence gathered was Level 3 and Level 4. Currently, there is no Level 1 and 2 evidence for this area, and further high-quality research is needed to conclude the growth of laparoscopic liver resection. Distinct from the Louisville statement 2008 and the Morioka consensus 2014, our current recommendations focus mainly on the treatment of HCC, a disease often accompanied by liver cirrhosis. These recommendations have arisen from combining evidence gathered from new studies and our experience in treating our patients with positive outcomes. The recommendations are meant to sustain the benefits of laparoscopic liver resection for HCC.

Disclosure Statement

The authors declare no conflicts of interest.

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