World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i17.4892

World J Gastroenterol 2014 May 7; 20(17): 4892-4899
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (15): Laparoscopic resection of gastrointestinal

Laparoscopic liver resections for hepatocellular carcinoma: Current role and limitations

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Received: November 26, 2013 Revised: January 8, 2014
Accepted: January 20, 2014
Published online: May 7, 2014

Abstract

Liver resection for hepatocellular carcinoma (HCC) is currently known to be a safer procedure than it was before because of technical advances and improvement in postoperative patient management and remains the first-line treatment for HCC in compensated cirrhosis. The aim of this review is to assess current indications, advantages and limits of laparoscopic surgery for HCC resections. We also discussed the possible evolution of this surgical approach in parallel with new technologies.

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Key words: Hepatocellular carcinoma; Laparoscopic liver resection; Hepatectomy; Minimally invasive; Review; Laparoscopic resection of gastrointestinal

Core tip: We assess in this review current indications, advantages and limits of laparoscopic surgery for hepatocellular carcinoma. We also discuss the possible evolution of this surgical approach in parallel with new technologies.

Gaillard M, Tranchart H, Dagher I. Laparoscopic liver resections for hepatocellular carcinoma: Current role and limitations. *World J Gastroenterol* 2014; 20(17): 4892-4899 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i17/4892.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i17.4892

INTRODUCTION

Hepatocellular carcinoma (HCC) represents the fifth most frequent cancer[1], and the third most widespread cause of cancer-related deaths in the world[2]. Most HCCs develop within chronic liver disease, mainly chronic hepatitis and cirrhosis. Screening for HCC among patients with chronic liver disease facilitates the early detection of small tumors, increasing the number of curative therapeutic options available. Liver transplantation appears most attractive since it treats both the cancer and the underlying disease. However, the scarcity of donors does not permit transplantation in all patients with early HCC[3]. Liver resection for HCC is currently known to be a safer procedure than it was before because of technical advances and improvement in postoperative patient management[4-7] and remains the first-line treatment for HCC in compensated cirrhosis in many centers.

Many types of liver resections, including major hepatectomies, are now performed by laparoscopy in specialized centers[8]. Since 2000, more than 600 cases of laparoscopic resection for HCC have been reported. Recent studies have confirmed that laparoscopic HCC resection is safe and seems to additionally improve the postoperative course particularly for cirrhotic patients[9-11]. Follow-up data from a few study groups have suggested that the long-term oncologic outcome has not been compromised by the laparoscopic approach compared with open resection[9,11-13].

The aim of this review is to assess current indications, advantages and limits of laparoscopic surgery for HCC resections. We also discussed the possible evolution of

this surgical approach in parallel with new technologies. The information in this review was extracted from the literature after a Medline search.

INDICATIONS AND CURRENT ROLE OF LAPAROSCOPY

There are presently no formalized indications for laparoscopic liver resection (LLR) and selection criteria may be varied among institutes. A consensus of experts who met in Louisville, Kentucky, United States in 2008, said the best indications for laparoscopy were solitary lesions, less than 5 cm, located in the anterior segments, at a distance from the line of transection, the hepatic hilum, and the vena cava[14]. Ever since this consensus conference took place, surgical indications have continued to evolve: tumor size on its own is no longer a contraindication to laparoscopic surgery[15] and experienced centers perform LLR for tumors in the posterior segments or central liver[16,17]. Although tumors should be located at a safe distance from the potential transection line on preoperative imaging, close proximity to the portal pedicle has also become a debatable limit as laparoscopic magnification allows very precise extrahepatic portal dissection[18]. Furthermore, a recent study by Yoon[19] show that LLR can be safely performed in selected patients with centrally located tumors close to the major hepatic veins, or the inferior vena cava. Of course, open approach is still required for some patients necessitating complex liver resection or additional procedures such as vascular or biliary reconstruction.

Most surgical teams consider non-compensated cirrhosis as a contraindication for liver resection and thereby for LLR[20]. An uncontrolled portal hypertension (esophageal varices > grade 1, platelet count < 8×10^{10} /L) is usually considered as an exclusion criterion for the laparoscopic approach[8]. Patients presenting an American Society of Anesthesiologists (ASA) score $\geqslant$ 3 and/or a major vascular invasion are also generally excluded[8]. Moreover, neither previous upper abdominal surgery[21] nor overweight is a contraindication to laparoscopic resection.

Although parenchymal-sparing resection is required by the presence of underlying liver disease, anatomic resection is preferred when liver surgery is performed with a curative intent for hepatocarcinoma due to the tumor's high propensity to invade the portal vein branches[22,23]. Indeed, anatomic resection independently improves long-term survival for patients with HCC, particularly in the case of tumors more than 2 cm in diameter[24]. Laparoscopy allows anatomical resections for HCC[20] with a previous control of portal pedicles including major hepatectomies[8]. Our team even advocated that atypical resections are paradoxically the most difficult and require previous experience in minor anatomic LLR (left lateral sectionectomy)[18].

Laparoscopy is well known for making subsequent surgical procedures easier since intra-abdominal adhesions are reduced after laparoscopic surgery compared with open surgery[20]. Although liver transplantation is considered the best treatment for patients with early HCC, resection may be the initial treatment in some patients, allowing salvage transplantation in case of delayed and limited recurrences within the Milan criteria, or being a selection tool providing complete information about the pathology and prognostic characteristics of the resected tumour, and thus facilitating the selection of the best candidates for further liver transplantation[25,26]. Performing the initial HCC resection by laparoscopy could facilitate a subsequent liver transplantation. In a study by Laurent *et al*[27], it has been shown that when the initial liver resection is done by laparoscopy, the subsequent salvage transplantation is associated with reduced operative time, blood loss, and transfusion requirements.

Screening and treatment of recurrence is another major issue. Repeated hepatectomy is a potentially curative therapy, and offers patients the possibility of long-term survival[28]. In a study by Dagher *et al*[8], re-resection after initial LLR was possible in 18.7% of recurrences. The difficulty of reintervention is increased by modifications of the anatomy and the formation of adhesions that can make a new surgical procedure more difficult and less safe. Two studies comparing laparoscopic and open redo surgery for recurrent HCC are available in the literature[29,30]. Laparoscopic redo procedure was associated with lower intraoperative blood loss, transfusion rates, postoperative morbidity, ascites and shorter hospital stay compared with open redo procedures whatever the initial approach. Moreover, the operating time for patients who underwent laparoscopic primary approach was significantly shorter compared to patients who were treated by primary open liver resection. With a minimally invasive approach, the formation of postoperative adhesions seems to be minimized, and the adhesiolysis procedure seems to be faster and safer in terms of blood loss and risk of visceral injuries, as previously reported[31]. Therefore, the laparoscopic approach for the treatment of HCC in cases of cirrhosis seems to be advisable as the first procedure whenever feasible.

OUTCOMES

Nineteen retrospective comparative studies of patients undergoing liver resection for HCC are available in the literature (Table 1), and five published meta-analysis have investigated the advantages and disadvantages of the LLR for HCC[32-36]. No randomized controlled trials comparing open to LLR have been reported.

Operative outcomes

LLR is associated with significantly less intraoperative blood loss and blood transfusion requirement, which can partly be explained by the hemostatic effect of pneumoperitoneum[18] and the magnified vision afforded by laparoscopy[9,18,34]. Besides, transfusion rates have been identi-

Table 1 Intraoperative outcomes in retrospective comparative studies concerning liver resection for hepatocellular carcinoma *via* laparoscopy or open approach

Ref.	Laparoscopies (*n*)	Median blood loss, mL			Blood transfusion			Median operative time, min		
		L	O	*P* value	L	O	*P* value	L	O	*P* value
Cheung *et al*[11], 2013	32	150	300	0.001	0%	4.7%	NS	204	232	NS
Kanazawa *et al*[10], 2013	28	88	505	0.0003	0%	4%	0.0379	228	236	NS
Lee *et al*[12], 2011	33	150	240	NS	6.1%	10%	NS	225	195	0.019
Ker *et al*[46], 2011	116	139	1147	< 0.001	6.9%	50.9%	< 0.001	156	190	NS
Hu *et al*[69], 2011	30	520 g	480 g	NS	-	-	-	180	170	NS
Kim *et al*[70], 2011	26	-	-	-	19.2%	24.1%	NS	147	220	0.031
Truant *et al*[13], 2011	36	452	447	NS	2.8%	3.8%	NS	193	215	NS
Tranchart *et al*[9], 2010	42	364	723	< 0.0001	9.5%	16.7%	NS	233	221	NS
Aldrighetti *et al*[71], 2010	16	258	617	0.008	4%	6%	NS	150	240	0.044
Belli *et al*[30], 2009	54	297	580	< 0.01	11%	25.6%	0.03	167	185	0.012
Lai *et al*[72], 2009	25	-	-	-	-	-	-	150	135	NS
Endo *et al*[73], 2009	10	-	-	NS	-	-	-	-	-	-
Sarpel *et al*[74], 2009	20	-	-	-	-	-	NS	161	165	NS
Belli *et al*[48], 2007	23	260	377	NS	0%	17.3%	0.036	148	125	0.016
Lee *et al*[75], 2007	25	100	250	0.012	4%	0%	NS	220	195	NS
Kaneko *et al*[76], 2005	30	350	505	NS	-	-	-	182	210	NS
Laurent *et al*[77], 2003	13	620	720	NS	4%	28.6%	NS	267	182	0.006
Shimada *et al*[78], 2001	17	400 g	800 g	NS	5.9%	10.5%	NS	325	280	NS

L: Laparoscopy; O: Open; NS: Non significant.

fied as an independent prognostic factor for disease-free survival in HCC[37,38], and blood loss was shown to be independently associated with recurrence and decreased survival rates after resection of HCC[39]. By decreasing the risk of transfusion, laparoscopy should improve the prognosis of patients undergoing liver resection for HCC[8].

Several transection devices, developed specifically for LLR, were reported[40-44]. However, the superiority of new hemostatic devices for parenchymal transection over the conventional clamp crushing method[45] has yet to be demonstrated. In a multicentric international retrospective study, Buell *et al*[43] advocated that stapler laparoscopic hepatectomy might provides several advantages including diminished blood loss and transfusion requirements however concerns existed regarding smaller surgical margins in the stapler hepatectomy group

In a recent study by Soubrane *et al*[20], conversion to laparotomy was necessary in 13% of 351 LLR performed for HCC in nine French tertiary centers. An underlying liver disease was observed in 85% of patients. The main cause for conversion was bleeding. It is important to note that conversion rates are not significantly different in patients with cirrhosis compared with non-cirrhotic patients, as reported by Dagher *et al*[8].

There was no significant difference in operative time in most studies[35], as observed in other indications.

Postoperative outcomes

Of all advantages of laparoscopy, the decrease of perioperative morbidity is paramount (Table 2). In a recent meta-analysis by Yin *et al*[35], postoperative morbidity rates after laparoscopic resections of HCC were significantly decreased compared with open surgery. Ker *et al*[46] have published the largest series and found a similar postoperative morbidity result. Postoperative outcomes identified in the recent French survey[20] found a 30-d postoperative mortality rate of 2% and an overall morbidity rate of 22%.

The main clinical advantage of laparoscopy for cirrhotic patients is probably the significantly lower rate of postoperative ascitic decompensation which was reported in four comparative studies[9,10,46-48] and three meta-analysis[32-34]. This finding could be explained by the preservation of portosystemic venous collateral circulation around the liver and parietal abdominal wall, limited mobilization and manipulation of the liver, restricted fluid requirements and decreased blood loss[34]. Cannon *et al*[49] advocated that the positive pressure of the pneumoperitoneum might exert a tamponade effect on bleeding from intra-abdominal varices which are a low pressure system, decreasing blood loss. Lower blood transfusion requirement is also an advantage of the laparoscopic approach in this very risky group of patients[9].

The incidence of liver failure was also reported as lower after LLR when compared to open liver resection[9,32,34]. No significant difference was reported regarding the incidence of other specific complications such as bile leakage and postoperative hemorrhage[10,32]. Concerning general complications, the rate of pulmonary complications appears significantly lower after laparoscopic resection[33].

Meta-analysis reporting on length of hospital stay are consistently favorable for LLR[32-36], consequently shortened by lower overall morbidity and incidence of intractable ascites.

Oncologic outcomes

The main concern about the use of laparoscopic procedure for malignancies is the risk of inadequate tumor resection. A positive histologic margin was associated with

Table 2 Oncologic outcomes in retrospective comparative studies concerning liver resection for hepatocellular carcinoma *via* laparoscopy or open approach

Ref.	Laparoscopies (*n*)	Positive surgical margin			Overall survival			Recurrence-free survival		
		L	O	*P* value	L	O	*P* value	L	O	*P* value
Cheung *et al*[11], 2013	32	-	-	-	76.6%[5]	57%[5]	NS	54.5%[7]	44.3%[7]	NS
Kanazawa *et al*[10], 2013	28	-	-	-	-	-	-	-	-	-
Lee *et al*[12], 2011	33	3.0%[1]	2.0%[1]	NS	76%[5]	76.1%[5]	NS	45.3%[7]	55.9%[7]	NS
Ker *et al*[46], 2011	116				62.2%[5]	71.8%[5]	NS	-	-	-
Hu *et al*[69], 2011	30	-	-	-	50%[5]	53.3%[5]	NS	-	-	-
Kim *et al*[70], 2011	26	3.8%[1]	3.4%	NS	-	-	-	84.6%	82.8%	NS
Truant *et al*[13], 2011	36	-	-	-	70%[5]	46%[5]	NS	35.5%[7]	33.6%[7]	NS
Tranchart *et al*[9], 2010	42	-	-	-	59.5%[5]	47.4%[5]	NS	60.9%[6]	54.3%[6]	NS
Aldrighetti *et al*[71], 2010	16	0%[1]	18.7%[1]	NS	-	-	NS	-	-	NS
Belli *et al*[30], 2009	54	0%[1]	40.8%[1]	NS	67%[4]	-	NS	52%[6]	-	NS
Lai *et al*[72], 2009	25	-	-	-	60%[4]	-	-	52%[6]	-	-
Endo *et al*[73], 2009	10	-	-	-	-	-	NS	-	-	NS
Sarpel *et al*[74], 2009	20	10%[1]	26.8%[1]	NS	-	-	NS	-	-	NS
Belli *et al*[48], 2007	23	8.6%[3]	0%[3]	NS	86.9%	82.6%	NS	-	-	-
Lee *et al*[75], 2007	25	-	-	-	-	-	NS	-	-	NS
Kaneko *et al*[76], 2005	30	-	-	-	61%[5]	62%[5]	NS	31%[7]	29%[7]	NS
Laurent *et al*[77], 2003	13	15.4%[1]	14.3%[1]	NS	89%[4]	55%[4]	0.04	46%[6]	44%[6]	NS
Shimada *et al*[78], 2001	17	41.2%[2]	50%[2]	NS	-	-	NS	-	-	-

[1]Tumor at surgical surface; [2]Tumor invasion < 5 mm; [3]Tumor invasion < 1 cm; Overall survival at 2, 3[4] or 5[5] years; Recurrence-free survival at 2, 3[6] or 5[7] years. L: Laparoscopy; O: Open; NS: Non significant.

a higher incidence of postoperative HCC recurrence[50], and a wide margin (2 cm) was reported to be preferable to the conventional 1-cm margin[51]. Most authors found that rates of positive margins after LLR were lower or similar to those after open hepatectomy, supporting that a good surgical margin is provided by the appropriate preoperative choice of the type of resection[9].

Laparoscopic surgery also was feared to increase the risk of peritoneal carcinomatosis and trocar-site deposits[52,53]. In the series reviewed in this study, we observed neither peritoneal carcinomatosis nor port-site recurrence.

Furthermore, in all studies comparing laparoscopic and open liver resection for HCC, there was no significant difference in recurrence-free or overall survival, suggesting that laparoscopic surgery does not compromise oncological principles (Table 3).

LIMITATIONS

Patient selection for laparoscopic hepatic resection is challenging but the most important prerequisite of good outcomes. Stringent selection criteria based on surgeon experience, patient clinical characteristics, lesion size and location must be employed. Thus, only 27% of patients with HCC who are candidates for resection could be operated *via* laparoscopy in an experienced team[9].

It was initially feared that laparoscopic liver resection would decrease the surgical margin due to the lack of palpation, except in the case of intra-abdominal hand-assisted LLR, though the haptic feedback transmitted through laparoscopic graspers is limited. However, manual exploration of cirrhotic liver can be difficult even during open surgery, and palpation probably is less important when an anatomic resection is planned. Intraoperative ultrasound should be systematically used to locate the tumor, making it possible to keep the intended margin. Therefore, a recent comparative study showed that sensitivity and specificity of intra-operative sonography were equivalent, whether performed *via* laparoscopy or laparotomy[54].

Fear of uncontrollable major bleeding or gas embolism explains the initial slow development of the laparoscopic approach. Nonetheless, there have not been any intra-operative deaths reported in the largest study on major LLR[55] and though frequent embolisms of CO_2 have been shown to occur[56], it is without any clinical repercussion, as shown in animal[57] as well as human studies[58].

The main criticism to LLR is its low reproducibility and its confinement in few expert centers. The reasons for such a limitation are 2-fold: the need of expertise in both laparoscopic and hepatic surgery and the expected long learning curve[14,59]. Vigano *et al*[60] observed a clear "learning curve" effect over a 13-year period of 60 procedures before a significant improvement in terms of operative time, conversion rate, blood loss, morbidity, and hospital stay, suggesting that LLR is reproducible in centers regularly performing liver surgery, but requires specific training in advanced laparoscopy.

PERSPECTIVES

Minimally invasive surgery

In an effort to make laparoscopy less and less invasive, surgeons have tried to decrease the number of trocars necessary to perform an operation. Several teams have reported their experience with single incision LLR for HCC[61,62]. The resections reported so far have mainly been small, atypical resections or left lobectomies, al-

Table 3 Postoperative outcomes in retrospective comparative studies concerning liver resection for hepatocellular carcinoma *via* laparoscopy or open approach

Ref.	Laparoscopies (*n*)	Postoperative morbidity			Ascites			Mean postoperative hospital stay, d		
		L	O	*P* value	L	O	*P* value	L	O	*P* value
Cheung *et al*[11], 2013	32	6.3%	18.8%	NS	31.1%	6.2%	0.871	4	7	< 0.0001
Kanazawa *et al*[10], 2013	28	10.7%	71.4%	< 0.0001	3%	18%	< 0.0001	10	19	< 0.0001
Lee *et al*[12], 2011	33	6.1%	24%	0.033	-	-	-	5	7	< 0.0005
Ker *et al*[46], 2011	116	6%	30.2%	< 0.001	1.7%	12.5%	0.002	6.2	12.4	0.001
Hu *et al*[69], 2011	30	13.3%	10%	NS	-	-	-	13	20	< 0.01
Kim *et al*[70], 2011	26	3.8%	24.1%	NS	-	-	-	11	16	0.034
Truant *et al*[13], 2011	36	25%	35.8%	NS	13.9%	22.6%	0.3	6.5	9.5	0.003
Tranchart *et al*[9], 2010	42	21.4%	40.5%	NS	7.1%	26.1%	0.03	6.7	9.6	< 0.0001
Aldrighetti *et al*[71], 2010	16	25%	43.7%	NS	0%	1%	NS	6.3	9	0.039
Belli *et al*[30], 2009	54	19%	36%	0.02	-	-	-	8.4	9.2	NS
Lai *et al*[72], 2009	25	16%	15%	NS	-	-	-	7	9	0.008
Endo *et al*[73], 2009	10	-	-	-	-	-	-	-	-	< 0.05
Sarpel *et al*[74], 2009	20	-	-	-	-	-	-	-	-	-
Belli *et al*[48], 2007	23	13%	47.8%	0.01	13%	39.1%	0.043	8.2	12	0.048
Lee *et al*[75], 2007	25	4%	4%	NS				4	7	< 0.001
Kaneko *et al*[76], 2005	30	10%	18%	NS	-	-	-	14.9	21.6	< 0.005
Laurent *et al*[77], 2003	13	36%	50%	NS	8%	36%	0.15	15.3	17.3	NS
Shimada *et al*[78], 2001	17	5.9%	10.5%	NS	-	-	NS	12	22	< 0.001

L: Laparoscopy; O: Open; NS: Non significant.

though in a recent case series, single port laparoscopic major hepatectomy was performed in 2 patients with HCC[62].

A few cases of Natural Orifice Translumenal Endoscopic Surgery LLR have also been reported[63]. However, this approach is still anecdotal.

The use of these minimally invasive approaches for more complex operations is certainly conceivable and will probably be extended with robotic assistance.

Robotic surgery

Robots are an inevitable part of the future of surgery and liver laparoscopy will undoubtedly follow along this road. Lai *et al*[64] reported the largest series of robot-assisted laparoscopic liver resection for HCC. In a subgroup analysis of minor liver resection, the robotic group had similar blood loss, morbidity rate, mortality rate, and R0 resection rate when compared with the conventional laparoscopic approach. However a significantly longer operative time was observed. Robotic assistance in liver surgery could clearly allow simplification of certain complex procedures such as major LLR and could facilitate additional procedures such as vascular or biliary reconstruction. It is possible that the learning curve for robotic resections may be shorter than that of conventional laparoscopic liver surgery, because the three dimensional imaging camera, wristed instruments, and better ergonomics will help already experienced laparoscopic surgeons to quickly familiarize themselves with the robotic procedure[65]. Most of the series reporting on robotic liver resection have focused on short-term perioperative outcomes. Long-term results and cost-effectiveness are necessary before the advantages and disadvantages of robotic liver resection can be conclusively stated.

Intra-operative guidance

LLR for small HCC remains a challenge because of limited tactile sensation, unidentifiable tumors, and complex liver anatomy. Therefore, intra-operative guidance during LLR is a future topic of interest. Intra-operative sonography has already been alluded to, but newer ingenious procedures to guide the surgeon are under investigation.

Innovations in this direction have actually been attempted. Chopra *et al*[66] reported five case of LLR under intra-operative MRI guidance in a porcine model without employing ferromagnetic material, and Kenngott *et al*[67] recently used robotic C-arm cone-beam computed tomography in a hybrid operating room for computer-assisted guidance during laparoscopic resection for HCC in man. Aside from some interferences between the camera and the magnetic field in the first study and additional radiation exposure for the patient and the need for the surgical team to leave the operating room while performing imaging in the second, the operations were performed under good conditions.

The use of fluorescent imaging technique for detecting HCC has also been reported. Ishizawa *et al*[68] have developed the use of indocyanine green (ICG), which has been intravenously injected for a preoperative liver function test, as a fluorescent source that enables the realtime identification of HCC during surgery. Since well or moderately differentiated HCC tissues retain portal uptake of ICG despite the lack of biliary excretion, small HCC located just beneath the liver surface were detected using a near-infrared light camera system, with high sensibility.

CONCLUSION

Review of the literature shows that in highly selected patients LLR for HCC seems to be superior to the open

liver resection in terms of perioperative results without compromising the oncological outcomes, especially in cirrhotic patients, in whom postoperative ascites is decreased by the use of laparoscopy. A prospective comparative study should be designed to confirm the advantages of laparoscopy for the management of HCC. The development of new technologies and robotics will certainly expand the use of laparoscopy in the multimodal management of hepatocarcinoma.

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P- Reviewers: Hsieh CC, Kikuchi L, Ko S **S- Editor**: Wen LL
L- Editor: A **E- Editor**: Wang CH