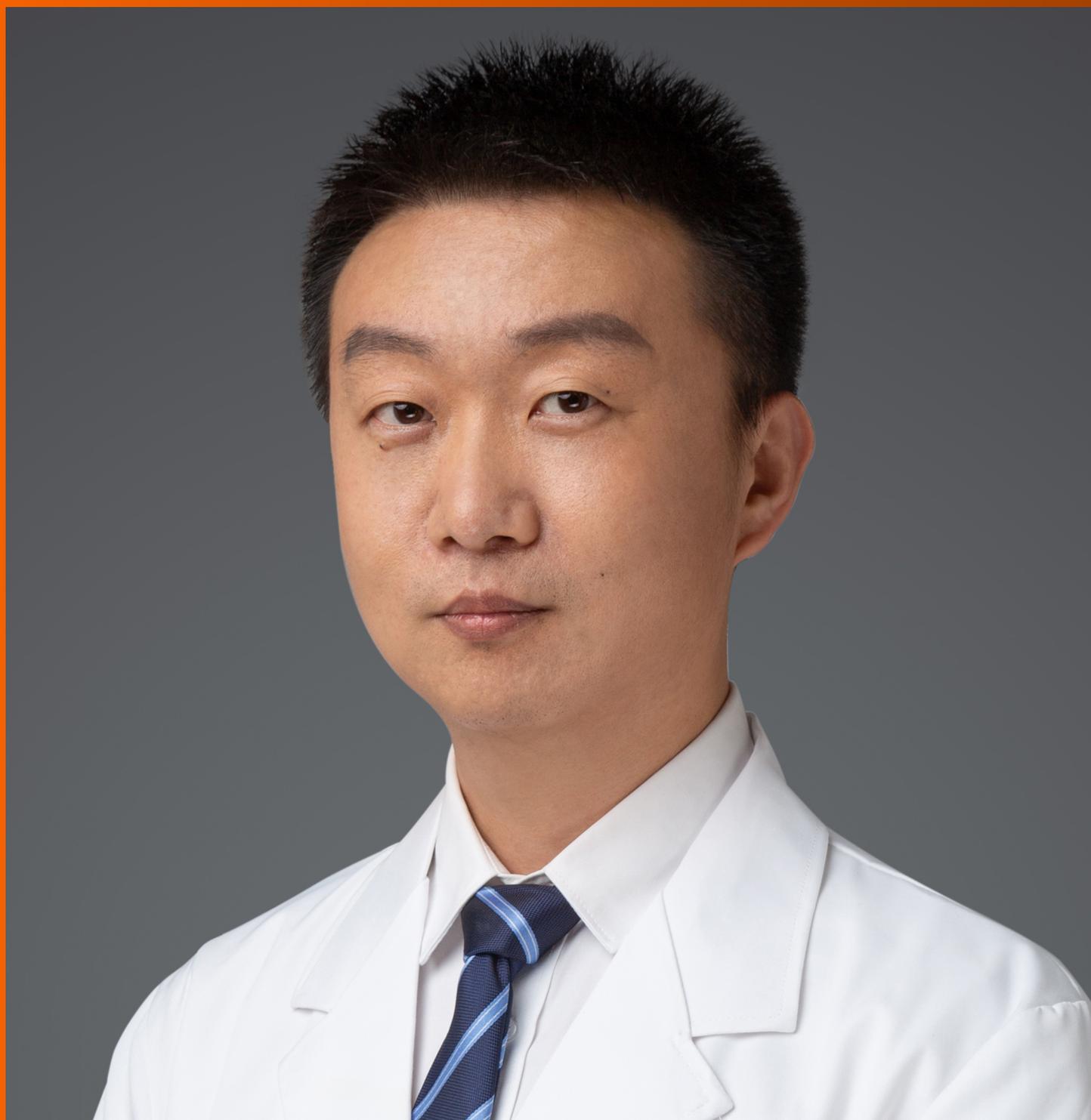


# World Journal of *Clinical Cases*

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**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Hong-Tao Xu, MD, PhD, Chief Physician, Professor, Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences of China Medical University, Shenyang 110001, Liaoning Province, China. xuht@cmu.edu.cn

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## Current status of radical laparoscopy for treating hepatocellular carcinoma with portal hypertension

Ze-Feng Shen, Xiao Liang

**ORCID number:** Ze-Feng Shen 0000-0003-0916-7555; Xiao Liang 0000-0002-7952-555X.

**Author contributions:** Shen ZF and Liang X designed the study and performed the literature search; all authors contributed to the preparation of the manuscript; All authors read and approved the final manuscript.

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**Ze-Feng Shen, Xiao Liang,** Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, Zhejiang Province, China

**Corresponding author:** Xiao Liang, MD, PhD, Professor, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, No. 3 East Qingchun Road, Hangzhou 310016, Zhejiang Province, China. [srrshlx@zju.edu.cn](mailto:srrshlx@zju.edu.cn)

### Abstract

The laparoscopic technique is clinically effective in treating hepatocellular carcinoma (HCC) with portal hypertension (PHT). However, existing studies lack systematic arrangement and induction. Here, we review the latest research advancement in laparoscopic technique for treatment of HCC with PHT, based on published literature and our single-institution experience. Our single-center experience reveals no statistical difference in both short- and long-term prognosis of HCC patients after laparoscopic liver resection (LLR), regardless of whether they suffer from PHT, which is consistent with previous studies on the use of LLR for HCC with PHT. Retrieval outcomes indicate existence of short- and long-term prognostic superiority, following laparoscopic treatment, relative to non-laparoscopic treatment. Besides that, LLR offers long-term prognostic advantage compared to laparoscopic radiofrequency ablation. In addition, we review the previous literature and propose corresponding perspectives on the therapy of hypersplenism, the utilization of Pringle maneuver, and the adoption of anatomical hepatectomy during radical laparoscopic treatment. HCC with PHT is not the "forbidden zone" of radical laparoscopic treatment. However, patients' preoperative liver function should be adequately estimated.

**Key Words:** Hepatocellular carcinoma; Portal hypertension; Radical laparoscopic treatment

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**Core Tip:** The manuscript presents the latest research advancement of laparoscopic technique for hepatocellular carcinoma (HCC) with portal hypertension (PHT) based on a combination of published literature and our single-institution experience. Consistent with previous studies of laparoscopic liver resection (LLR) for HCC with PHT, our single-institution experience showed that there exists no statistical difference

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in both short-term and long-term prognosis of HCC patients after LLR, regardless of whether they suffer from PHT. Retrieval outcomes indicated the possession of short-term and long-term prognostic superiority after laparoscopic treatment compared with non-laparoscopic treatment, and long-term prognostic advantage after LLR compared with laparoscopic radiofrequency ablation, respectively. In addition, this manuscript reviews previous studies and proposes corresponding perspectives on the therapy of hypersplenism, the utilization of Pringle maneuver, and the adoption of anatomical hepatectomy during radical laparoscopic treatment.

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## INTRODUCTION

Among the most frequent and malignant tumors globally, hepatocellular carcinoma (HCC) ranks sixth in morbidity and third in mortality<sup>[1]</sup>. China is home to approximately 18.4% of the world's population and accounts for more than half of all HCC cases worldwide. Specifically, 365000 new cases and 319000 HCC-related deaths occur annually in China<sup>[2,3]</sup>. Most HCC cases gradually evolve from cirrhosis, with portal hypertension (PHT) reportedly one of the most prominent clinical manifestations during the decompensation period<sup>[4,5]</sup>. Patients diagnosed with HCC and PHT have a dramatically poor long-term prognosis (5-year overall survival < 50%), owing to a deficiency of effective treatment therapies<sup>[6]</sup>. By virtue of the complicated condition and superior difficulty of surgical operations, there is a lack of consensus regarding the most effective alternative modalities for HCC patients with PHT. Nevertheless, previous studies were generally based upon the foundation of conventional laparotomy. The laparoscopic technique, which involves laparoscopic hepatectomy and laparoscopic radiofrequency ablation, offers patients and surgeons minimal invasion, less postoperative complications, and higher surgical quality, relative to open surgery. Indeed, the efficacy of laparoscopy for treating HCC with cirrhosis has been extensively described<sup>[7]</sup>. However, its therapeutic strengths for HCC patients with PHT remains unclear. In this article, we comprehensively review the latest research on use of the laparoscopic technique for treating HCC with PHT based on a combination of published literature and our single-institution experience.

## THE GENERATIVE MECHANISM OF HCC WITH PHT

Between 70%-90% of all HCC cases develop from post-hepatic cirrhosis, which has been certified as the principal etiology contributing to HCC with PHT<sup>[8]</sup>. Hepatic sinusoids narrowed or occluded by compression of pseudolobules and regenerative nodules, diffuse fibrosis in hepatic tissue, interrupt the bloodstream, subsequently increasing the portal venous pressure (PVP). Apart from that, generation and deterioration of PHT in HCC patients has also been implicated in pathogenesis<sup>[9]</sup>. Firstly, blood in HCC cases is primarily supplied by the hepatic artery. However, abundant arteriovenous short circuits crisscross the tumors, affecting bloodstream from the high-pressure hepatic artery to the portal system and causing deterioration of clinical symptoms in HCC with PHT. Secondly, the biological mechanism of HCC determines the vulnerability of portal vein to tumorous invasion. Additionally, obstruction of neoplastic thrombus, coupled with compression of cancerous tissues, has been shown to aggravate the detrimental effects of PHT. Furthermore, therapeutic techniques for treating HCC, such as hepatic lobectomy and transcatheter arterial chemoembolization, can arouse the transient addition of PVP.

## PHT DIAGNOSIS

Due to the arduousness of direct measurement, PVP is represented by the difference between wedged and free hepatic venous pressure, which is also known as hepatic venous pressure gradient (HVPG). The recognized criterion for diagnosing PHT requires that HVPG does not exceed 10 mmHg (1 mmHg = 0.133 kPa) under normal conditions. Otherwise, patients are confronted with the hazards of PHT<sup>[9,10]</sup>. However, HVPG measurement is seldom adopted in clinical practice owing to the traumas associated with examination and the stringent requirements to manipulators' technique. Consequently, surgeons tend to diagnose and evaluate PHT based on clinical manifestations, physical signs, laboratory tests, radiography, and gastroscopy. The indirect PHT diagnostic criteria, as proposed by Bayraktar *et al*<sup>[11]</sup>, still possesses referential value, comprising the following items: (1) Megalosplenism (the longitudinal axis > 13 cm following ultrasonography); (2) Thrombocytopenia (< 100 × 10<sup>9</sup>/L) and (or) leukocytopenia (< 4.0 × 10<sup>9</sup>/L) over three consecutive times; (3) Diameter of the portal vein > 14 mm or splenic vein > 10 mm under ultrasonography; (4) Esophageal or gastric varices diagnosed by gastroscopy; and (5) Abdominal dropsy.

Recently, progress has been made in the use of non-invasive diagnosis for PHT. Generally, the use of transient elastography (TE) and magnetic resonance imaging (MRI) has generated excellent prospects for clinical application that may substitute for HVPG measurement. These advancements indicate that during estimation of hepatic stiffness using FibroScan, TE is an effective diagnostic technique for both hepatic fibrosis and cirrhosis as well as PHT<sup>[12]</sup>. The powerful post-processing technology preponderances of MRI reveal a superior application prospect, although there is need for further studies in MRI-based PVP estimation. The complicated spatial anatomic relationship among blood vessels in the portal vein system can be plainly presented by utilizing portography and three-dimensional imaging technology. For instance, hepatic perfusion imaging can immediately reflect PVP by comparing the perfusion volume discrepancy among hepatic parenchyma, hepatic artery, and portal vein. Furthermore, when combined with hemodynamic information such as bloodstream direction, velocity, and flow, the technique can mirror the variations in bloodstream parameters of the portal vein and its tributaries<sup>[13,14]</sup>.

## CURRENT STATUS ON APPLICATION OF RADICAL NON-LAPAROSCOPIC TECHNIQUE FOR TREATING HCC WITH PHT

Liver transplantation, radiofrequency ablation, and hepatectomy are considered radical therapies for HCC<sup>[15]</sup>. Functionally, liver transplantation can simultaneously resolve problems associated with both HCC and PHT. However, limited donated organs, coupled with their rapid deterioration during the waiting period have greatly restricted its clinical application<sup>[15,16]</sup>. On the other hand, radiofrequency ablation (RFA) used to be a palliative remedy. With the development of imaging positioning technology, ablation morphology and regulation, RFA has achieved radical treatment of unifocal small HCC. In deep-seated HCC patients with a tumor diameter ≤ 3 cm, RFA reportedly reveals the inconspicuous distinction in survival rate but less influence on liver function and PVP, relative to hepatectomy<sup>[17-20]</sup>. However, its curative effects significantly diminish when cancerous focus exceeds 5 cm in diameter or displays the "heat sink effect" approaching macro-vascular. Although hepatectomy is the most fundamental radical treatment for HCC, its efficacy and safety remains controversial, especially following PHT. For example, previous studies have reported a reduction in the number of hepatic sinuses, which further aggravate clinical manifestation of PHT and exacerbate the negative effects of esophageal gastric-fundus variceal bleeding, refractory ascites, and hepatic failure following hepatectomy. Based on these issues, the American Association for the Study of Liver Disease and the European Association for the Study of the Liver guidelines have regarded HCC with PHT as the "forbidden zone" of hepatectomy and conversely recommended use of ablation therapy<sup>[16,21]</sup>.

Numerous studies have shown that implementation of hepatectomy should not be so conservative. In eastern countries, PHT is not considered an absolute contraindication to hepatectomy. In fact, many eastern researchers have demonstrated the potential to achieve low postoperative mortalities and morbidities, provided liver function is thoroughly estimated before the procedure. This has subsequently been approved by the guidelines for diagnosis and treatment of HCC in Asian multi-regions<sup>[22-24]</sup>. Particularly, correlational studies<sup>[25,26]</sup> show that the American Association for the Study of Liver Disease and the European Association for the Study of the Liver

guidelines are based on small sample sizes, which is contrary to many recent findings proposed by western centers<sup>[27,28]</sup>. For example, Santambrogio *et al*<sup>[27]</sup> demonstrated that hepatectomy offers long-term survival and alleviates impairment of liver function in HCC patients with PHT and Child-Pugh A5 class (preserved liver function).

Despite the lack of consensus, it is evident that the aforementioned controversies are biased towards non-laparoscopic treatment therapies, such as open liver resection (OLR). During decision-making for selection of the most effective therapeutic approach for treating HCC with PHT, clinicians need to consider the possibility of laparoscopic treatment. This is because therapeutic laparoscopy is superior to non-laparoscopic techniques, as evidenced by minimal invasion, less postoperative complications, and higher surgical quality. It is possible that laparoscopic hepatectomy, the so-called compromise method, may settle the existing disputes on hepatectomy during treatment of HCC with PHT.

## CURRENT STATUS ON APPLICATION OF RADICAL LAPAROSCOPIC FOR TREATMENT OF HCC WITH PHT

Numerous studies have demonstrated the benefits of minimally invasive technique in cirrhosis-related HCC associated cases<sup>[7,29]</sup>. Generally, laparoscopic surgery has been shown to possess additional advantages for patients with cirrhosis and chronic liver disease by reducing liver compression manipulation, abdominal wall impairment, and extensive hepatic mobilization. All these help conserve collateral blood and lymphatic circulation, minimize dangers associated with postoperative esophageal gastric-fundus variceal bleeding, refractory ascites, and hepatic failure, as well as reduce total postoperative morbidities<sup>[30]</sup>. Several studies have reported lack of statistical differences in both short- and long-term prognosis of HCC patients following therapeutic laparoscopy, such as laparoscopic liver resection (LLR) and LRFA, irrespective of whether or not they suffer from PHT, the primary clinical manifestation of decompensated cirrhosis. Some retrospective case-control studies expounded on the feasibility and effectiveness of LLR, based on perioperative and long-term consequences of HCC with clinically significant PHT. Their findings revealed no statistically significant differences in overall survival (OS) between the PHT and non-PHT groups. In fact, none of the subjects in the PHT group died within the first year following LLR<sup>[6,31]</sup>.

We recruited 156 HCC patients who underwent LLR at our Hepato-Pancreatic-Biliary Surgery Department between February 2016 and September 2019. We divided them into PHT ( $n = 26$ ) and non-PHT ( $n = 130$ ) groups based on presence or absence of PHT. The PHT group was associated with a series of indicators reflecting liver dysfunction ( $P < 0.05$ ). Previous studies, in particular, tended to consider liver function-related characteristics comprising aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum albumin, prothrombin time, Child-Pugh grade, and indocyanine green retention rate at 15 min (ICG-R15) as confounding factors, and they thus included them into propensity score matching (PSM) analysis. These characteristics are substantially correlated with the severity of PHT, and the behavior of the classifying characteristics mentioned above as confounding factors will make it such that the PHT group faced fewer hazards of PHT, while the non-PHT group was subjected to worse liver dysfunction. Consequently, we did not incorporate the liver function-related characteristics into the PSM analysis. Our results revealed significant differences between the groups with regard to prothrombin time (PHT > non-PHT,  $P = 0.021$ ), international normalized ratio (PHT > non-PHT,  $P = 0.015$ ), and platelet count (PHT > non-PHT,  $P = 0.015$ ) following PSM ( $n = 48$ ). We found homogeneity ( $P > 0.05$ ) in ALT, AST, and other liver function-related characteristics as well as intraoperative blood loss, postoperative complication, and other perioperative courses. In addition, Kaplan-Meier curves revealed 3-year OS rates of 66.5% and 78.4% in PHT and non-PHT groups, respectively, following PSM, although these differences were not statistically significant ( $P = 0.5506$ )<sup>[32]</sup>. To summarize, appropriate implementation of laparoscopic technique could further stretch the indications of liver resection, and HCC with PHT is not in the "forbidden zone" of LLR. The premise for LLR manipulation requires that patients' preoperative liver function should meet corresponding criteria, which comprises Child-Pugh grade A or B, remnant liver volume > 40%, and ICG-R15  $\leq 45\%$ <sup>[33]</sup>. Other laparoscopic techniques, such as LRFA, may be an alternative choice for treating HCC with PHT. A previous study reported similar OS rates between the two groups ( $P = 0.857$ ) following PSM analysis and based on cumulative curves of OS rates stratified by PHT status in HCC patients after RFA<sup>[34]</sup>.

Because this review concentrates on therapeutic laparoscopy for HCC with PHT, published short- and long-term consequences of laparoscopy *vs* non-laparoscopy will be discussed in detail. In summary, two authors independently identified and retrieved articles describing radical laparoscopic treatment for HCC with PHT from electronic databases, namely Web of Science, PubMed, Ovid, and Cochrane Library, from their inception to November 2020. Search strategy was (portal hypertension OR hypertension, portal OR liver cirrhosis OR ascites OR hypersplenism OR esophageal and gastric varices) AND (liver neoplasms OR adenoma, liver cell OR carcinoma, hepatocellular OR intrahepatic cholangiocarcinoma OR hepatocellular carcinoma OR hepatic carcinoma OR hepatic cancer OR hepatic tumors OR liver carcinoma OR liver cancer OR liver tumors) AND (endoscopy OR endoscopes OR laparoscopes OR laparoscopy). Retrieved articles were included in the analysis if they met the following inclusion criteria: (1) Explicitly indicated that the enrolled cases comprised HCC patients with PHT (all or partial). To be more specific, if the retrieved article indicated that all patients were subjected to HCC with PHT, the article would be included and marked as "All patients are HCC with PHT (All)"; if the retrieved article stated categorically that none of the patients suffered PHT, the article was excluded; if all the patients in the retrieved article had to endure the misery of HCC with cirrhosis, while only some patients were subjected to HCC with PHT, the article was included and marked as "Part of the patients are HCC with PHT (Partial)"; if not all the patients in the retrieved article suffered HCC with cirrhosis, the article was excluded to prevent excessive heterogeneity; and (2) Compared short- and long-term efficacy of various anti-HCC therapies for HCC with PHT, and at least one experimental group underwent radical laparoscopic treatment.

Finally, 12 studies met the inclusion criteria and were included in the analysis. The OS rates retrieved from the 12 studies comparing therapeutic efficacy of various anti-HCC therapies for HCC with PHT patients are outlined in [Table 1](#). The vast majority of patients involved in the included articles had evolved from post-hepatic liver cirrhosis, but different causes of liver cirrhosis had no significant effect on the long-term prognosis. We defined PHT and non-PHT group according to the description in the included articles. In reality, only two articles used the combination of HVPG measurement and non-invasive tests to diagnose PHT, and the majority merely used non-invasive tests, as described in [Table 1](#). In summary, 5-year OS ranged from 38% to 90% when therapeutic laparoscopy was used, although there were no statistically significant differences between the laparoscopy and non-laparoscopy groups. Conversely, patients who underwent laparoscopy exhibited superior intraoperative and postoperative outcomes relative to those under non-laparoscopy ([Table 2](#)). A comparison between the techniques indicated that LLR was superior to LRFA with regards to long-term prognostic outcomes ([Tables 1 and 2](#)).

### **Rate of conversion to laparotomy**

In cases where there are insurmountable difficulties during therapeutic laparoscopy, or continuation of surgical operation exposes the patients to hazards, it is essential to convert timely to laparotomy. Based on the included studies, we found conversion rates of laparoscopic hepatectomy to laparotomy that ranged from 0% to 27.6%. Generally, LLR is a relatively original technique that requires surgeons to experience a steep learning curve before proficient manipulation<sup>[35,36]</sup>. Therefore, it is necessary for practitioners to accumulate a laparoscopic experience of 45-75 cases to accomplish the "rising period" of the learning curve. In addition, more knowledge is required when such complicated conditions as HCC combined with PHT are encountered<sup>[37,38]</sup>. Even surgeons who are proficient in laparoscopic hepatectomy need to consider conversion to laparotomy under the following situations: (1) Abdominal cavity infection, extensive abdominal adhesion, laparoscopic separation and exposure difficulties, or intraoperative severe hemorrhage caused by forced separation; (2) Discovery of multiple intrahepatic, intraperitoneal, and hilar lymph node metastasis after pneumoperitoneum; (3) Immense tumors affecting the exposure and dissection of the first and second hepatic portal; and (4) Uncontrollable massive bleeding (> 2000 mL)<sup>[39,40]</sup>.

### **Intraoperative blood loss and transfusion requirements**

HCC patients with PHT tend to suffer worse coagulation function and variceal hemorrhage relative to those in the non-PHT group<sup>[32]</sup>, indicating that intraoperative hemorrhage is a key factor that significantly limits utilization of hepatectomy during treatment of HCC patients with PHT. Morise *et al*<sup>[41]</sup> reported a blood loss between 200 and 700 mL in patients with HCC and chronic liver disease based on a retrospective analysis of 21 studies. Although the average blood loss after OLR is within this range,

**Table 1 Overall survival rates obtained from research articles comparing therapeutic efficacy between laparoscopy and non-laparoscopy for treatment of hepatocellular carcinoma patients with portal hypertension**

Ref.	Country	Number of patients	Proportion of cirrhosis	Causes and their proportion of liver cirrhosis	Diagnostic method of PHT	Proportion of PHT	1-yr overall survival	3-yr overall survival	5-yr overall survival	Statistical significance
Di Sandro <i>et al</i> <sup>[42]</sup> , 2018	Italy	LLR/OLR, 75/75	All	Virus/Alcohol/Virus + Alcohol/Other, 92/24/16/18	Non-invasive tests	PartialLLR ≈ OLR	LLR/OLR, 98%/90%	LLR/OLR, 76%/68%	LLR/OLR, 60%/58%	NSD
Le Roux <i>et al</i> <sup>[67]</sup> , 2017	France	LLR/OLR, 38/24	All	Virus/Alcohol/NASH/Other, 6/29/21/6	Non-invasive tests	PartialLLR ≈ OLR	NA	NA	NA	NA
El-Gendi <i>et al</i> <sup>[60]</sup> , 2017	Egypt	LLR/OLR, 25/25	All	Virus, 50	Non-invasive tests	PartialLLR ≈ OLR	NA	NA	NA	NA
Tarantino <i>et al</i> <sup>[40]</sup> , 2017	Italy	LLR/OLR, 13/51	All	Virus/Alcohol/NASH/Other, 59/1/2/2	HVPG + Non-invasive tests	PartialLLR ≈ OLR	NA	NA	NA	NA
Sposito <i>et al</i> <sup>[61]</sup> , 2016	Italy	LLR/OLR, 43/43	All	Virus/Other, 67/19	Non-invasive tests	Partial	LLR/OLR, 98%/88%	LLR/OLR, 75%/79%	LLR/OLR, 38%/46%	NSD
Harada <i>et al</i> <sup>[43]</sup> , 2016	Japan	LLR/OLR, 20/48	All	Virus/Other, 58/10	Non-invasive tests	All	LLR/OLR, 100%/98%	LLR/OLR, 90%/68%	LLR/OLR, 90%/54%	NSD
Memeo <i>et al</i> <sup>[48]</sup> , 2014	France	LLR/OLR, 45/45	All	Virus/Alcohol, 64/26	Non-invasive tests	PartialLLR ≈ OLR	LLR/OLR, 88%/63%	LLR/OLR, 59%/44%	LLR/OLR, 12%/22%	NSD
Truant <i>et al</i> <sup>[39]</sup> , 2011	France	LLR/OLR, 36/53	All	Virus/Alcohol/Other, 17/55/17	HVPG + Non-invasive tests	PartialLLR ≈ OLR	LLR/OLR, 98%/85%	LLR/OLR, 80%/64%	LLR/OLR, 70%/46%	NSD
Belli <i>et al</i> <sup>[44]</sup> , 2009	Italy	LLR/OLR, 54/125	All	Virus/Other, 175/4	Non-invasive tests	PartialLLR ≈ OLR	LLR/OLR, 94%/94%	LLR/OLR, 67%/62%	NA	NSD
Berger <i>et al</i> <sup>[68]</sup> , 2018	America	LRFA/ORFA, 478/177	All	NA	Non-invasive tests	All	NA	NA	NA	NA
Casaccia <i>et al</i> <sup>[50]</sup> , 2017	Italy	LLR/LRFA, 22/24	All	Virus/Alcohol/Virus + Alcohol/Other, 33/9/1/2	Non-invasive tests	Partial	LLR/LRFA, 96%/88%	LLR/LRFA, 84%/54%	LLR/LRFA, 70%/32%	SD
Santambrogio <i>et al</i> <sup>[69]</sup> , 2015	Italy	(LLR+OLR)/LRFA, 76/76	All	Virus/Other, 122/30	Non-invasive tests	Partial	(LLR + OLR)/LRFA, 94%/88%	(LLR + OLR)/LRFA, 82%/62%	(LLR + OLR)/LRFA, 69%/48%	SD

HCC: Hepatocellular carcinoma; HVPG: Hepatic venous pressure gradient; LLR: Laparoscopic liver resection; NA: Not available; NASH: Non-alcoholic steatohepatitis; NSD: No significant difference; OLR: Open liver resection; PHT: Portal hypertension; SD: Significant difference.

individual patients may suffer severe hemorrhage. Despite existence of selection bias, numerous studies have affirmed that LLR is superior to OLR with regards to intraoperative blood loss and transfusion requirements<sup>[42-44]</sup>, which is partly attributed to hemostatic efficacy of pneumoperitoneum and magnified visual field under laparoscopy<sup>[45,46]</sup>. Theoretically speaking, utilization of pneumoperitoneum during

**Table 2** Intraoperative and postoperative outcomes obtained from articles comparing therapeutic efficacy between laparoscopy and non-laparoscopy for treatment of hepatocellular carcinoma patients with portal hypertension

Ref.	Number of patients	Minor hepatectomy, < 3 adjacent segments	Major hepatectomy, ≥ 3 adjacent segments	Conversion laparotomy rate	Operative blood loss	Transfusion requirements	Margins, cm	R0 resection rate	Operative time	Length of stay	Complications
Di Sandro <i>et al</i> <sup>[42]</sup> , 2018	LLR/OLR, 75/75	LLR/OLR, 74/73	LLR/OLR, 1/2	0 (0)	LLR < OLR	Equivalent	LLR > OLR	Equivalent	Equivalent	LLR < OLR	LLR < OLR
Le Roux <i>et al</i> <sup>[67]</sup> , 2017	LLR/OLR, 38/24	LLR/OLR, 25/23	LLR/OLR, 13/1	NA	Equivalent	NA	NA	NA	NA	LLR < OLR	LLR < OLR
El-Gendi <i>et al</i> <sup>[60]</sup> , 2017	LLR/OLR, 25/25	NA	NA	0 (0)	Equivalent	Equivalent	Equivalent	Equivalent	Equivalent	LLR < OLR	Equivalent
Tarantino <i>et al</i> <sup>[40]</sup> , 2017	LLR/OLR, 13/51	LLR/OLR, 13/51	NO	3 (23.1%)	Equivalent	NA	NA	Equivalent	Equivalent	LLR < OLR	LLR < OLR
Sposito <i>et al</i> <sup>[61]</sup> , 2016	LLR/OLR, 43/43	LLR/OLR, 42/41	LLR/OLR, 1/2	2 (4.7%)	Equivalent	NA	Equivalent	Equivalent	Equivalent	LLR < OLR	LLR < OLR
Harada <i>et al</i> <sup>[43]</sup> , 2016	LLR/OLR, 20/48	LLR/OLR, 20/45	LLR/OLR, 0/3	NA	LLR < OLR	Equivalent	NA	NA	LLR < OLR	NA	Equivalent
Memeo <i>et al</i> <sup>[48]</sup> , 2014	LLR/OLR, 45/45	LLR/OLR, 43/43	LLR/OLR, 2/2	NA	Equivalent	Equivalent	NA	NA	LLR < OLR	LLR < OLR	LLR < OLR
Truant <i>et al</i> <sup>[39]</sup> , 2011	LLR/OLR, 36/53	LLR/OLR, 36/53	NO	7 (19.4%)	Equivalent	Equivalent	Equivalent	NA	Equivalent	LLR < OLR	Equivalent
Belli <i>et al</i> <sup>[44]</sup> , 2009	LLR/OLR, 54/125	LLR/OLR, 51/86	LLR/OLR, 3/39	4 (7.4%)	LLR < OLR	LLR < OLR	LLR > OLR	LLR > OLR	LLR < OLR	Equivalent	LLR < OLR
Berger <i>et al</i> <sup>[68]</sup> , 2018	LRFA/ORFA, 478/177	NA	NA	NA	NA	NA	NA	NA	LRFA < ORFA	LRFA < ORFA	LRFA < ORFA
Casaccia <i>et al</i> <sup>[50]</sup> , 2017	LLR/LRFA, 22/24	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Santambrogio <i>et al</i> <sup>[69]</sup> , 2015	(LLR+OLR)/LRFA, 76/76	NA	NA	8 (27.6%)	NA	NA	NA	NA	NA	NA	NA

HCC: Hepatocellular carcinoma; LRFA: Laparoscopic radiofrequency ablation; LLR: Laparoscopic liver resection; NA: Not available; OLR: Open liver resection; ORFA: Open radiofrequency ablation; PHT: Portal hypertension; R0: Complete excision with all margins negative.

hepatectomy effectively reduces venous hemorrhage, with difficulties caused by positive central venous pressure during liver transection surmounted. The intraoperative CO<sub>2</sub> pneumoperitoneum pressure is 7-10 times higher than central venous pressure, which is generally 12 mmHg. Thus, pneumoperitoneum can effectively alleviate venous exudation in a hermetic space. Furthermore, meticulous

anatomy of liver parenchyma under laparoscopy may also enhance hemostasis<sup>[47]</sup>. Unprecedented clarity during magnification supported by high-definition cameras allows for accurate clipping of all the slight blood vessels, which is unimaginable during laparotomy, and sophisticated anatomical implements for laparoscopy, such as laparoscopic clips and electricity-driven staplers, enable surgeons to manipulate hemostasis smoothly and precisely.

### **Surgical margins and the R0 resection rate**

Attaining negative resection (R0) margins is a key target of oncological surgery. To date, however, only Belli *et al*<sup>[44]</sup> has shown that LLR has a statistically superior R0 rate than OLR. Other studies have also obtained favorable outcomes in LLR, although these were not statistically significant. Several studies have indicated that LLR can acquire wider resection margins compared to OLR<sup>[42,44]</sup>. We investigated this and found the presence of particular selection bias. It is a tendency to select LLR for HCC with PHT patients who undergo more malignant and complicated tumors; then the surgeons expand the margins during laparoscopic surgery to attain R0 resection<sup>[42]</sup>. Besides, the magnified visual field under laparoscopy can also help to ameliorate the accuracy of resection.

### **Operative time**

Previous studies have put forward conflicting conclusions regarding the therapeutic modality with the least operative time, owing to multiple factors, such as operative experience, institutional equipment, and patient-specific condition. While some propose that LLR takes less operative time than OLR<sup>[43,44,48]</sup>, a majority have found no significant differences in the time taken by these two surgical procedures. Further exploration indicates that studies that reported on patients with smaller-diameter tumors persevere in less operative time than LLR. Understandably, minor LLR is easily implemented when neither extensive hepatic mobilization nor vessels manipulation is involved, which explains the short operative time. Conversely, major LLR requires accumulation of abundant experience, which demands extensive hepatic mobilization and retraction of the hepatic parenchyma. Hence, the operative time of laparoscopic therapy with major hepatectomy will be significantly prolonged.

### **Postoperative complications and length of hospital stay**

Almost all studies, with the exception of Belli *et al*<sup>[44]</sup> who persisted on the equivalence of the nosocomial length of stay (LOS) between LLR and OLR while merely taking major hepatectomy into account, have reported that LLR results in a significantly shorter LOS. Generally, LOS is accompanied by presence of postoperative complications. Particularly, fewer general complications, such as aspiration pneumonia, peptic ulcer, cardiac arrhythmia, and renal failure, as well as surgical complications, including wound infection, wound dehiscence, and intra-abdomen bleeding, are attributed to the superiority of this technology on less manipulation-related abdominal wall trauma and higher surgical quality, following therapeutic laparoscopy<sup>[49]</sup>. In fact, LLR significantly reduces retraction of the subcostal musculature, relative to OLR, whose immense hockey stick-like incision transects the abdominal muscle under the costal margin, thereby alleviating postoperative complications and reducing LOS.

### **Long-term survival**

Although the preponderances of LLR, relative to OLR, with regards to short-term prognosis have been extensively studied, a majority of the included studies have proposed that both techniques are capable of generating equivalent long-term prognosis ( $P > 0.05$ ). This necessitates further exploration by restricting confounding factors and prolonging follow-up time.

Casaccia *et al*<sup>[50]</sup> compared OS probabilities in HCC patients with PHT after LLR or LRFA, after a 72-mo follow up period, and found that LLR had significantly higher ( $P = 0.048$ ) survival rates (44.2%) than LRFA (26.1%). This inferior OS probability was attributed to the fact that LRFA causes portal vein violations and inadequate ablation of the primary lesion, although LLR can simultaneously resolve the problems of both primary lesion and portal vein violations.

## OTHER CONTROVERSIES ON RADICAL LAPAROSCOPIC TREATMENT

### **Disputes on the therapy of hypersplenism**

Hypersplenism is the clinical manifestation of PHT, but relieving PHT cannot resolve hypersplenism. The impaired coagulation and immune function of HCC and hypersplenism patients make surgical operation extremely traumatic and risky. Nevertheless, patients merely utilizing hepatectomy have to suffer the gradual aggravation due to the continuous existence of postoperative hypersplenism, with erythrocytes, granulocytes, and megakaryocytes proceeding to degrade. Hence, the treatment of hypersplenism is particularly momentous, and the superiorities and inferiorities of various approaches are as follows. The postoperative complications of transcatheter splenic arterial embolization are slighter and more controllable, and the immune system is not destroyed owing to the retention of the adequate spleen. Spleen radiofrequency ablation can also rectify hypersplenism and preserve the immunological function of the spleen, while its safety and accuracy are still debatable points. Relatively uncomplicated and short time-consuming, splenectomy can surmount the coagulation and immune dysfunction caused by hypersplenism. Given its preponderance, hepatectomy combined with splenectomy and devascularization is deemed the preferred therapy for the treatment of HCC with hypersplenism.

Nevertheless, the simultaneous utilization of open hepatectomy and splenectomy (OHS) means that HCC with hypersplenism patients have to endure severe surgical trauma resulted by an immense inverse L-shaped incision. Li *et al*<sup>[51]</sup> proved the superior short-term prognosis of laparoscopic hepatectomy and splenectomy (LHS) over OHS *via* clinical investigation, and observation indexes favoring LHS included postoperative complications probability, LOS, and visceral function. These investigators consequently insisted that LHS eliminated relevant contraindications and was a superb minimally-invasive surgery with high security and effectiveness for HCC with hypersplenism. Adopting LRFA rather than LLR as the anti-HCC therapy, Hu *et al*<sup>[52]</sup> put forward that the 1-year and 21-mo disease-free survival after laparoscopic RFA and splenectomy were 78.8% and 61.4%, respectively, which were comparable to those of OHS<sup>[53,54]</sup>.

Dong *et al*<sup>[55]</sup> guaranteed that there existed no statistical difference between the groups in the selection of anti-HCC therapies (comprising LLR and LRFA) and merely investigated and contrasted the security and effectiveness of laparoscopic splenectomy *vs* open splenectomy for HCC with hypersplenism. Despite the equivalent outcome of operative time, the laparoscopic splenectomy group acquired better achievements than open splenectomy group in the following evaluation indicators: Intraoperative blood loss and transfusion requirements, postoperative complication probability, and postoperative LOS. Thus, the viewpoint that the laparoscopic splenectomy group can achieve better short-term prognosis in contrast with open splenectomy group has been explicitly testified, but the comparison of their long-term prognosis needs further research.

### **Disputes on the utilization of Pringle maneuver**

Portal triad clamping (Pringle maneuver), the earliest and easiest technique utilized to control intraoperative hemorrhage during hepatic operation, was derived from the method of pinching and pressing the hepatoduodenal ligament with fingers to control bleeding, which was reported by Pringle *et al* in 1908. In virtue of its relative simplicity and effectiveness in implementation, Pringle maneuver and its derivatives are still extensively manipulated now. Numerous hepatobiliary surgeons will choose the typical Pringle maneuver or selective hepatic vascular occlusion to reduce intraoperative hemorrhage while performing major hepatectomy. Pringle maneuver can be applied continuously or intermittently. Demanding a 5-min reflow after every blocking hepatic blood inflow for 15-20 min, the intermittent Pringle maneuver utilized repeatedly can relatively prolong the time of hepatic ischemia tolerance and reduce the hepatic ischemia-reperfusion injury<sup>[56]</sup>. Nevertheless, the intermittent Pringle maneuver may lead to additional bleeding during the hepatic reflow, and the mere intermittent compression of the liver wound with gauze may not be adequate hemostasis, especially in the case of deep-seated HCC<sup>[57]</sup>. As for continuous Pringle maneuver, if the hepatic blood inflow is blocked beyond a specific time limit, thermal ischemia and subsequent reperfusion injury are more likely to cause irreversible damage to the remaining hepatic parenchyma<sup>[58]</sup>. Nowadays, it is believed that the healthy liver, even the cirrhosis liver with sufficient compensation, can endure the thermal ischemia injury caused by vascular occlusion under ordinary temperature for 30 min<sup>[59]</sup>. When the estimated time of hepatic blood inflow interruption exceeds 30

min, most surgeons will select the application of intermittent Pringle maneuver<sup>[59]</sup>.

Regarding HCC combined with PHT, there exists no direct study on the security and effectiveness of Pringle maneuver during hepatectomy (including laparotomy and laparoscopy). Before hepatectomy, most researchers have subjectively determined whether to implement Pringle maneuver or not according to patient conditions. Tarantino *et al*<sup>[40]</sup> opposed the usage of Pringle maneuver during segmental and non-anatomic hepatectomy<sup>[40]</sup>. Partially coincident with the standpoints of El-Gendi *et al*<sup>[60]</sup> and Sposito *et al*<sup>[61]</sup> also recommended that the Pringle maneuver should be utilized in the case of massive intraoperative hemorrhage. However, the latter restricted the supporting role of Pringle maneuver during LLR, while the former did not. Different from the perceptions above, Xu *et al*<sup>[62]</sup> routinely utilized Pringle maneuver intermittently regardless of LLR or OLR, taking into consideration controlling intraoperative hemorrhage is the priority. Their results showed that the Pringle maneuver time of LLR was statistically longer than that of OLR, which reflected the feasibility but complexity of Pringle maneuver executed during LLR in contrast with OLR.

### **Disputes on the adoption of anatomical hepatectomy**

Whether to use anatomical hepatectomy for HCC with PHT patients, each center adheres to its respective guiding ideology. Some centers support anatomical hepatectomy regardless of LLR or OLR, suggesting that anatomical hepatectomy should be implemented as far as possible<sup>[42,50,61]</sup>, while some directly adopt non-anatomic hepatectomy without any explanation<sup>[43,60]</sup>. Through the retrospective study, Cheung *et al*<sup>[36]</sup> found that OLR and LLR were generally anatomic and non-anatomic, respectively, which might be related to the higher requirements of laparoscopic anatomical hepatectomy. Research shows that anatomical hepatectomy can simultaneously resect initial lesions along with micrometastasis and preserve the volume of the functional liver to the greatest extent, which decreases the risk of postoperative hepatic failure and provides the reoperation possibility of the recurrent foci<sup>[63]</sup>. But anatomic hepatectomy demands strictly grasping the operative indication; otherwise, it cannot benefit patients and will cause adverse surgical consequences. At present, the existing evidence suggests that anatomical hepatectomy is mainly applicable to primary HCC without the invasion of large blood vessels, whose diameters range between 2-5 cm<sup>[64]</sup>. For HCC with a diameter greater than 5 cm, there is no significant difference between anatomic and non-anatomic hepatectomy in OS and disease-free survival. Under those circumstances, tumorous biological behaviors (*e.g.*, tissue differentiation and microvascular invasion) have become the main constraints affecting the survival rate, which offset the influence of surgical procedure selection<sup>[64,65]</sup>. Despite the technical maturity of laparoscopic hepatectomy, laparoscopic anatomical hepatectomy is still not extensively popularized owing to its requirements of high-level laparoscopic anatomy technique, especially during the hepatectomy of specific areas, such as section VII and VIII. Clinical practices have proven that the application of intraoperative ultrasound can locate the branch distribution of hepatic vein, and the coordination of ultrasonic knife and cavitron ultrasonic surgical aspirator can achieve the meticulous dissection of hepatic vein trunk and its branches, all of which contribute to averting excessive intraoperative injury and hemorrhage during laparoscopic hepatic parenchyma disconnection.

## **CONCLUSION**

Previous research has demonstrated that hepatectomy causes high incidence of post-hepatectomy liver failure in HCC with PHT patients. However, a considerable number of patients have been found to tolerate hepatectomy, which subsequently generates superior therapeutic outcomes relative to other approaches<sup>[24,66]</sup>. To manage the potential controversies associated with hepatectomy for treatment of HCC patients with PHT, clinicians are advised to consider the possibility of laparoscopic surgery. Our single-institution experience revealed no statistically significant differences in both short- and long-term prognosis of HCC patients after LLR, regardless of whether they suffer from PHT or not, which is consistent with previous studies on LLR for HCC with PHT<sup>[6]</sup>. HCC with PHT is not the "forbidden zone" of LLR, but patients' preoperative liver function should be adequately estimated *via* Child-Pugh grade, remnant liver volume, and ICG-R15.

Results from our review, which compared short- and long-term efficacy of radical laparoscopic treatment with other anti-HCC therapies for HCC with PHT, indicated

that LLR is superior to OLR with regards to short-term prognosis and also has long-term prognostic advantages relative to LRFA.

This review also discusses other controversies on radical laparoscopic treatment and puts forward the following perspectives. The simultaneous utilization of laparoscopic hepatectomy and splenectomy can obtain better short-term prognosis for HCC with hypersplenism patients. Regarding HCC combined with PHT, results reflect the feasibility but complexity of Pringle maneuver executed during LLR in contrast with OLR. Anatomical hepatectomy can decrease the risk of postoperative hepatic failure and provides the reoperation possibility of the recurrent foci. Still, laparoscopic anatomical hepatectomy is of superior difficulty, especially in the case of HCC combined with PHT, which demands the coordination of intraoperative ultrasound, ultrasonic knife, and cavitron ultrasonic surgical aspirator.

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