Surgical Endoscopy (2019) 33:2916–2926
https://doi.org/10.1007/s00464-018-6593-2

Laparoscopic versus open mesohepatectomy for patients with centrally located hepatocellular carcinoma: a propensity score matched analysis

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Received: 19 July 2018 / Accepted: 13 November 2018 / Published online: 29 November 2018

Abstract

Background Although laparoscopic mesohepatectomy (LM) has been performed for patients with centrally located hepatocellular carcinoma (CL-HCC), its short- and long-term benefits compared with traditional open surgery remain unclear. The aim of the present study was to explore the independent role of LM in the prognosis of patients with CL-HCC.

Methods A retrospective analysis was undertaken of 348 patients who underwent mesohepatectomy for CL-HCC between January 2012 and October 2017 in our hospital. The impact of the surgical methods on long-term prognosis was evaluated by multivariable regression analysis. In addition, patients in the LM group were matched in a 1:3 ratio with open mesohepatectomy (OM) group.

Results Some 307 patients underwent OM and 41 had LM. In both adjusted and non-adjusted models, patients in LM group had similar overall survival (OS, both $P > 0.05$) and disease-free survival (DFS, both $P > 0.05$) compared to OM patients. The mean (s.d.) OS in LM and OM groups was 41.6 (7.2) and 46.4 (1.4) months, respectively. The mean (s.d.) DFS in LM and OM groups was 37.7 (5.9) and 33.4 (1.5) months, respectively. After propensity score-matched (PSM) analysis, 96 patients remained in OM group and 32 patients in LM group. In the PSM subset, patients in LM group still had comparable OS ($P = 0.120$) and DFS ($P = 0.757$) compared to patients in the OM group. After PSM, patients receiving LM had longer vascular exclusion time ($P = 0.006$) and shorter hospital stay ($P = 0.004$). In addition, LM was associated with reduced postoperative morbidity after PSM adjustment ($P = 0.026$).

Conclusions LM is associated with fewer complications and does not compromise survival compared with OM. LM can be recommended as a safe and reasonable surgical option in selected patients with CL-HCC.

Keywords Hepatocellular carcinoma · Mesohepatectomy · Laparoscopy · Prognosis

Liver resection has an important role in the management of centrally located hepatocellular carcinoma (CL-HCC) [1, 2]. Though technically challenging, parenchyma-sparing mesohepatectomy is still widely used for its preservation of liver parenchyma with the potential for decreasing the risk of postoperative liver dysfunction or failure [3]. Laparoscopic hepatectomy, since firstly reported in 1990s [4], has been shown to be a promising technique [5, 6]. In previous studies, patients undergoing laparoscopic hepatectomy had shorter operation time, less blood loss and shorter hospital stay [7–10]. However, due to the technical complexities, laparoscopic hepatectomy is predominately recommended in patients undergoing left lateral sectionectomy or wedge resection [11, 12].

With advances in laparoscopic instruments and techniques, laparoscopic mesohepatectomy (LM) has been

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00464-018-6593-2) contains supplementary material, which is available to authorized users.

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reported in several publications. Gumbs et al. and Yoon et al. described the total laparoscopic central hepatectomies in 2008 and 2009, respectively [13, 14]. Machado et al. reported an entirely laparoscopic LM using an intrahepatic Glissonian approach in 2011 [15]. In a case series published in 2014, Satoshi et al. reported a favorable outcome of LM in 32 patients [16]. However, no comparison was carried out in this study. Therefore, further studies exploring the advantages and disadvantages of LM technique are still needed.

Due to the tumor heterogeneity of CL-HCC, the surgical procedures of LM may vary considerably in different centers. We have established a classification for patients with CL-HCC based on tumor position and its relationship to vascular structures in 2013, and these patients can be divided into four subgroups according to it [17]. In the present study, we aimed to compare the short- and long-term outcomes for CL-HCC treated with either LM or open mesohepatectomy (OM) in matched cohorts. Confounding factors including tumor classification were adjusted by the propensity score-matched (PSM) analysis.

Patients and methods

Study population

We retrospectively reviewed 880 consecutive patients who underwent hepatectomy for CL-HCC between January 2012 and October 2017 in West China Hospital, Sichuan University. To clarify the pure prognostic impact of LM among patients who were treatable by either LM or OM, 532 patients were excluded due to the following reasons: (1) patients with recurrent tumor ($n = 23$); (2) patients with coexisting peripherally located tumors ($n = 83$); (3) patients undergoing extended hemi-hepatectomy ($n = 92$); (4) patients with R1 resection ($n = 6$); (5) tumors only requiring resection of one Couinaud's segment ($n = 145$); (5) history of other malignancy ($n = 15$); (6) history of preoperative transcatheter arterial chemoembolization, radiofrequency ablation or chemoradiotherapy ($n = 88$); and (7) incomplete prognostic data ($n = 80$). Data of the remaining 348 patients were analyzed in detail. Thirty-two patients comprised the cases (LM) and were matched in a 1:3 ratio with OM controls selected from patients who had undergone mesohepatectomy at the same period. The HCC diagnosis was confirmed by histopathology. This study was approved by Ethical Committee of the West China hospital.

Liver function evaluation

For patients undergoing mesohepatectomy, liver function should meet the following criteria: indocyanine green retention rate at 15 min (ICG-R15) below 15%. Additionally, according to the definition of Johnson et al. [18], the albumin–bilirubin (ALBI) grade was used to evaluate underlying liver function for patients with CL-HCC. The equation for the linear predictor was as follows: linear predictor = (log10 bilirubin × 0.66) + (albumin × − 0.085). Patients were divided into grade 1–3 by the cut points of linear predictor. The cut points were as follows: ≤ − 2.60 (ALBI grade 1), − 2.60 to − 1.39 (ALBI grade 2), and > − 1.39 (ALBI grade 3).

Classification for CL-HCC

According to our classification established in 2013 [17], patients with CL-HCC were divided into four subgroups based on tumor location and the relationship between tumor and vascular structures. The extent of liver resection was different in four types [17, 19]. Type I was defined as tumor arising from segments V and IVb. In type I, tumors are usually adjacent to or directly invade large vessels in the first porta hepatis. Type II was defined as tumor arising from segments VIII and IVa (close to or direct invasion of the second portal structures). Type III referred to tumor between segments IVa and VIII and segments V and IVb, which was not adjacent to neither portal branches. Type IV was defined as tumor that occupied a large proportion of the parenchyma between the first and second portal hepatis. In type IV, tumors were usually adjacent to or direct invasion of both portal structures. In this type, to obtain tumor clearance, segment IV, V, VIII ± I should be resected (Fig. 1).

Operative procedures

The hepatic vascular ultrasonography, contrast-enhanced thoracic, abdominal and pelvic computed tomography (CT) and/or magnetic resonance imaging (MRI) were carried out to evaluate the resectability of tumor. The intraoperative ultrasound was also routinely performed after liver mobilization in both LM and OM groups. The selection of surgical methods (LM or OM) was based on a comprehensive evaluation of indicators including tumor number, size, location, residual liver volume and underlying liver function.

Surgical procedures for mesohepatectomy were described before [17, 20]. Both LM and OM were undertaken by using the fissure for ligamentum teres hepatic (LTH) approach. In this approach, the round ligament was used as the symbol for isolating and dividing the Glisson's pedicles of the removed part. For standard mesohepatectomy (segment IVa + IVb + V + VIII), the Glisson's pedicle of segment IV was cut along the right edge of the fissure for the round ligament firstly and after that the left resection line appeared along the falciform ligament. The liver parenchyma (left side) was transected just to the right of the falciform ligament down to the direction of IVC and then continued just

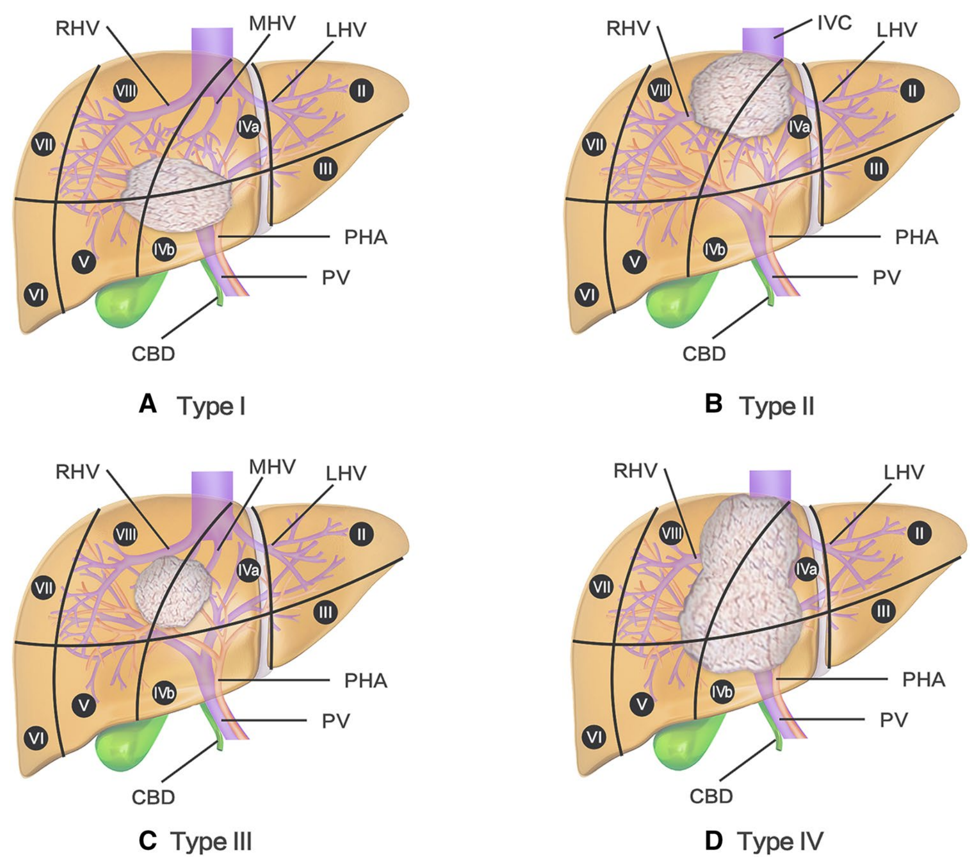

Fig. 1 Classification of centrally located hepatocellular carcinoma: **A** type I, **B** type II, **C** type III and **D** type IV. *RHV* right hepatic vein, *LHV* left hepatic vein, *MHV* middle hepatic vein, *PHA* proper hepatic artery, *PV* portal vein, *CBD* common bile duct, *IVC* inferior vena cava

to the left edge of the middle hepatic vein (MHV). After that, the right anterior pedicle was isolated, encircled and clamped. Finally, liver transection of the right side was carried out along the demarcation line between the right anterior and the right posterior sectors. (The right hepatic vein was used as a landmark.) In order to obtain outflow control, the MHV can be ligated or stapled before parenchyma transection of the right side.

In a laparoscopic hepatectomy (Fig. 2), the patient was usually placed in a supine position or mild reverse Trendelenburg position (French position). The primary surgeon stood between the legs with two assistants (one was scopist) on left side of the patient, while all instruments were placed on the right side of the patient. A telescope port was inserted in the periumbilical region. Pneumoperitoneum was maintained at 12 mmHg. Two main working 12-mm ports were inserted where the subcostal area met the midclavicular line and epigastric area (left side of the xiphoid process), respectively. A 5-mm port was placed in the subcostal area where it met the right anterior axillary line. Another 5-mm port was inserted in the left edge of the left rectus abdominis (Fig. 3). Liver parenchyma transection was carried out under the guidance of intraoperative ultrasonography. The Pringle maneuver (PM) was utilized during the procedure especially in LM. Harmonic scalpel (Ethicon Endo-Surgery, USA), cavitron ultrasonic aspiration (CUSA, Valleylab, Inc, USA) and or LigaSure (ValleyLab, Inc, USA) were used for transection of hepatic parenchyma.

Definitions

Anatomic resection was defined according to the study of Makuuchi et al. [21]. Postoperative mortality was defined as death within 90 days after surgery. All complications were classified based on the Clavien–Dindo classification [22]. Microvascular invasion (MVI) was defined as vascular (vein or artery) or lymphatic invasion (identification of tumor cells within endothelial-lined spaces on standard hematoxylin and eosin stained slides) [23]. Liver failure was defined as an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5 [24]. Bile leakage referred to a drain fluid-to-serum total bilirubin concentration ratio ≥ 3.0 [25]. Ascites was defined as abdominal drainage that was more than 500 mL/day and lasting longer than 3 days. Pulmonary infection was defined by a positive sputum cultures and/or alteration of chest radiography and/or CT scan outcomes associated with fever and hyperleukocytosis [26]. Surgical site infection was defined based on Centers for Disease Control and Prevention (CDC)'s National Nosocomial Infection Surveillance (NNIS) system [27].

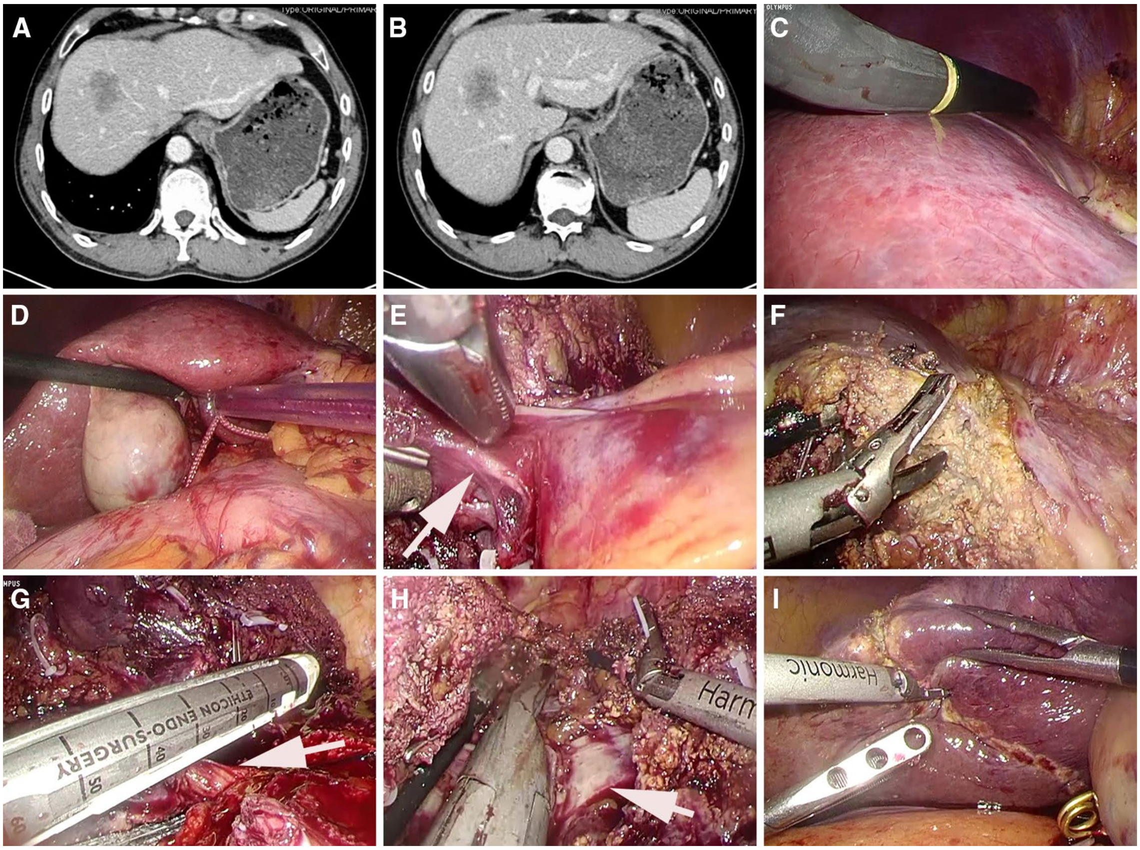

Fig. 2 Surgical procedures of laparoscopic mesohepatectomy in one patient. **A, B** Enhanced computed tomography pictures indicating a patient with centrally located tumor; **C** laparoscopic ultrasonography; **D** Pringle maneuver; **E** isolating and dividing the portal pedicle of left medial lobe; arrow: portal pedicles of left medial lobe; **F** parenchyma dissection of the left side; **G** isolating and dividing the portal pedicles of right anterior lobe; **H** the middle hepatic vein transection; **I** parenchyma dissection of the right side

Follow-up

Patients were followed up at a 2-month interval in the first year after discharge from hospital and at a 3-month interval thereafter. At each follow-up visit, all patients underwent laboratory examinations including liver function, alpha fetoprotein (AFP) level, and HBV-DNA level (for patients infected with hepatitis B virus), and an abdominal ultrasound. A contrast-enhanced MRI or CT was carried out once every 6 months or earlier if recurrence was suspected. The time of overall survival (OS) was calculated from the date of operation to the last follow-up or until death. The time of disease-free survival (DFS) was calculated from the date of operation to the date, when recurrence was confirmed by imaging examinations.

Statistical analysis

Continuous variables were presented as mean ± SD and tested by *t* test or Kruskal–Wallis *H* test. Categorical variables were expressed as frequency (%) and tested by Chi-square test or Fisher's exact test. Survival outcomes including OS and DFS were analyzed using the Kaplan–Meier method and were compared using log-rank tests. Using multivariate Cox proportional hazards regression models, we calculated hazard ratios (HRs) and 95% confidence intervals (CI) for LM versus OM in patients with CL-HCC. Confounding factors were selected based on the following criteria: the variable was related to the main predictor (surgical method) or the dependent factors (surgical outcomes), and it was not in the causal pathway between the outcomes and the main predictor. In adjusted models, we adjusted for covariates that changed HR or β by at least 10%, when they were added to or removed from the model [28]. PSM was performed based on the following variables: patient demographics (age and sex), tumor characteristics (tumor number, size, classification, encapsulation, differentiation and MVI) and liver function (ALBI and ICG-R15). Patients in the LM group were matched to those in the OM group with a matching ratio of 1:3 with the closest estimated propensity score within 0.2 of the standard deviation of the logit-transformed propensity score. All statistical

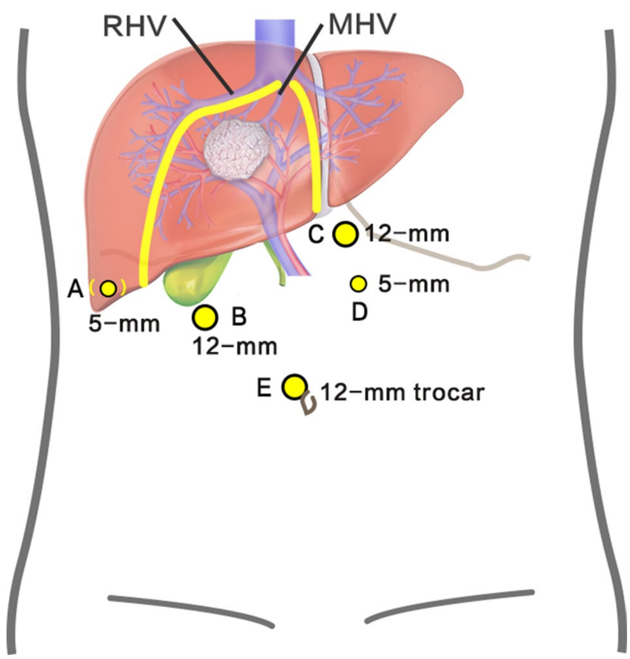

Fig. 3 Port positioning for total laparoscopic mesohepatectomy. A and D two assistant 5-mm ports; B and C two main working 12-mm ports (completing the parenchymal transection and controlling blood flow of the middle hepatic vein); E telescope port

analyses were performed by R (http://www.R-project.org) and EmpowerStats software (http://www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Patient characteristics and short-term outcomes

Patients undergoing LM had different distributions of tumor classification compared to those who underwent OM. Thirty-two patients (78.0%) in LM group were in type III, and no patients in type IV underwent LM. In addition, patients who underwent LM had smaller tumor size ($P<0.001$) and earlier tumor stage ($P=0.008$). The other characteristics including age, gender, preoperative liver function indicators (in terms of serum levels of albumin, aspartate aminotransferase, alanine aminotransferase, prothrombin time, platelet count, ICG-R15 and ALBI), tumor number, AFP level, encapsulation, differentiation and incidence of viral hepatitis had no significant differences between two groups (all P values >0.05) (Table 1).

Surgical procedures performed in two groups are shown in detail in Table 2. The duration of operation, estimated blood loss, blood transfusion requirement, postoperative peak prothrombin time and total bilirubin levels were comparable between LM and OM groups (all P values >0.05) (Table 2). Patients in LM group had longer vascular exclusion time ($P=0.049$), lower postoperative peak alanine aminotransferase (ALT, $P=0.028$) and aspartate aminotransferase (AST, $P=0.023$) levels and shorter postoperative hospital stay ($P=0.016$). The LM group exhibited a lower rate of postoperative morbidity than the OM group before adjustment, but without statistical significance (14.6% vs. 21.5%, $P=0.416$). The details of complications are listed in Table 3. In addition, the incidence of overall postoperative mortality was similar between two groups ($P=0.616$). There was no postoperative death in LM group, while one patient in OM group died from postoperative liver failure.

Long-term outcomes of LM vs. OM

The median follow-up period was 20 (range 1–72) months. The univariable survival analysis (Supplementary Table 1) showed the non-adjusted long-term outcomes of LM versus OM groups. Patients in LM group had similar OS ($P=0.374$) and DFS ($P=0.083$) compared to patients in OM group. The mean (s.d.) OS in LM and OM groups was 41.6 (7.2) and 46.4 (1.4) months, respectively. The 1-, 2- and 3-year OS rates were 97.0%, 92.9% and 46.5% for LM group and 87.1%, 77.1% and 73.8% for OM group, respectively. The mean (s.d.) DFS in LM and OM groups was 37.7 (5.9) and 33.4 (1.5) months, respectively. The 1-, 2- and 3-year DFS rates were 86.9%, 79.0% and 39.5% for LM group and 72.5%, 61.1% and 53.8% for OM group, respectively. The other prognostic factors in univariable analysis are shown in detail in Supplementary Table 1.

As shown in Table 4, after adjusting potential confounding factors, no significant differences in OS (HR, 0.6; 95% CI 0.2–2.3; $P=0.487$) and DFS (HR, 0.7; 95% CI 0.3–1.9; $P=0.550$) were observed between two groups.

Outcomes after LM and OM in propensity score adjusted population

As shown in Supplementary Tables 2 and 3, in the matched cohort, all potential prognostic covariates were similar (all P values >0.05). The distributions of propensity scores in two matched groups were also similar (data not shown). The intra- and postoperative parameters are shown in Supplementary Table 2. After PSM, patients in LM group still had longer vascular exclusion time ($P=0.006$) and shorter hospital stay ($P=0.004$). In the current study, after PSM, the LM group had lower overall postoperative morbidity rate compared to the OM group (9.4% vs. 27.1%; $P=0.026$), while postoperative mortality rates showed no significant difference after PSM adjustment.

In the PSM cohort, patients in LM group still showed similar OS ($P=0.120$) and DFS ($P=0.757$) compared to patients in OM group (Fig. 4). The 1-, 2- and 3-year OS

Table 1 Clinical features of the 348 patients with centrally located hepatocellular carcinoma

	OH ($n=307$)	LH ($n=41$)	P value
Sex (female/male)	39/268	9/32	0.107
Age (years)	54.3 ± 12.1	53.2 ± 11.1	0.586
ICG-R15 (%)	6.0 ± 4.2	6.5 ± 5.9	0.645
Preoperative ALT (IU/L)	50.3 ± 44.5	43.1 ± 27.9	0.314
Preoperative AST (IU/L)	47.6 ± 38.9	41.6 ± 27.7	0.337
Preoperative total bilirubin (μmol/L)	16.8 ± 18.5	15.4 ± 6.3	0.625
Preoperative albumin (g/L)	41.1 ± 4.1	42.0 ± 4.0	0.163
ALBI (grade 1/2/3)	142/156/5	22/17/1	0.350
Platelet (10^9/L)	134.0 ± 59.6	131.7 ± 52.6	0.817
Prothrombin time (s)	12.3 ± 1.2	12.1 ± 1.1	0.189
AFP (ng/mL)	665.1 (0.8–66836.0)	299.8 (1.0–1210.0)	0.420
HBsAg (P/N)	261/45	31/10	0.111
HBV-DNA (copies/mL)			0.111
< 1000	45 (14.7%)	10 (24.4%)	
≥ 1000	261 (85.3%)	31 (75.6%)	
Tumor size (cm)	5.7 ± 3.0	4.0 ± 2.0	< 0.001
Tumor number (single/multiple)	223/84	35/6	0.080
Classification (I/II/III/IV)	111/65/74/57	5/3/32/0	< 0.001
AJCC7 T-stage (T1/T2/T3)	255/32/20	41/0/0	0.008
Major vascular tumor thrombus (no/PV/HV/both)	279/14/5/1	41/0/0/0	0.405
MVI (no/yes)	195/58	35/6	0.308
Tumor encapsulation			0.255
Encapsulated	225 (73.3%)	34 (82.9%)	
Non-encapsulated	82 (26.7%)	7 (17.1%)	
Differentiation (high/moderate/low)	30/233/44	9/26/6	0.097

Data are shown as mean ± SD or median (range) or *n* (%)

Total number of patients equals the number of patients with konwn clinicopathologic data (shown in the Table) plus the number of cases with unknown cinicopathlogic data

OH open hepatectomy, *LH* laparoscopic hepatectomy, *ICG-R15* indocyanine green retention rate at 15 min, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALBI* albumin–bilirubin, *AFP* alpha fetoprotein, *HBV* hepatitis B virus, *PV* portal vein, *HV* hepatic vein, *MVI* microvascular invasion, *Y* yes, *N* no

rates were 96.3%, 91.2% and 68.4% for LM group and 95.3%, 93.6% and 90.5% for OM group, respectively. The 1-, 2- and 3-year DFS rates were 84.0%, 72.0% and 36.0% for LM group and 87.2%, 75.6% and 59.7% for OM group, respectively. In the PSM cohort, after adjusting confounders (screened in the primary cohort), no significant differences were confirmed in OS ($P=0.473$) and DFS ($P=0.119$) between two groups (Table 4).

Discussion

Previous publications have shown that laparoscopic approach was a safe option for minor liver resection, especially left lateral sectionectomy and wedge resection. It was usually related to a smaller wound, shorter operation duration, less blood loss and shorter length of stay [8, 9, 11, 12]. In the Morioka consensus meeting, laparoscopic left lateral sectionectomy has been recommended to be a standard practice due to the quicker recovery after laparoscopic hepatectomy [12]. However, LM remains a controversial technique for patients with CL-HCC, due to the perceived technical complexity of liver resection and the high risk of difficult-to-control bleeding. In addition, there is no studies related to oncologic features of LM in previous studies. In the present study, we observed that CL-HCC patients undergoing LM had a similar long-term prognosis compared to patients who underwent OM. However, after PSM, patients who underwent LM had a shorter hospital stay and less morbidity than those after OM.

In this study, some major confounding factors such as liver function (ICG-R15 and ALBI), tumor classification, tumor stage and anatomic resection were controlled by multivariable analysis and PSM method. The liver function was evaluated by ICG-R15 and ALBI grade. There were many published studies on ICG clearance in various

Table 2 Surgical procedures and operation related parameters

	OH ($n=307$)	LH ($n=41$)	P value
Resected segments	V + IVb:VIII + IVa:V + VIII:IVa + IVb:IV + V + VIII ± I = 91:40:42:31:103	V + IVb:VIII + IVa:V + VIII:IVa + IVb:I V + V + VIII = 6:5:7:9:14	0.108
Anatomic resection (yes/no)	223/84	32/9	0.584
Duration of operation (min)	175.0 ± 37.3	173.3 ± 55.1	0.813
Intraoperative blood loss (mL)	395.8 ± 361.9	328.2 ± 328.0	0.272
Duration of vascular exclusion (min)	33.7 ± 19.4	41.3 ± 18.8	0.049
Intraoperative transfusion (no/yes)	230/28	39/2	0.398
Transfusion volume (mL)	105.2 (0.0–2250.0)	41.5 (0.0–1200.0)	0.236
Postoperative peak ALT (IU/L)	538.8 ± 526.9	388.4 ± 340.7	0.028
Postoperative peak AST (IU/L)	518.5 ± 589.1	387.8 ± 452.2	0.023
Postoperative peak PT (s)	15.4 ± 6.9	13.7 ± 1.8	0.180
Postoperative peak TB (μmol/L)	39.5 ± 33.4	40.6 ± 36.6	0.841
Postoperative hospital stay (day)	12.8 ± 5.1	10.8 ± 4.1	0.016
90-day mortality (no/yes)	306/1	41/0	0.616

Data are shown as mean ± SD or median (range) or n

Total number of patients equals the number of patients with konwn clinicopathologic data (shown in the Table) plus the number of cases with unknown cinicopathlogic data

OH open hepatectomy, *LH* laparoscopic hepatectomy, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *PT* prothrombin time, *TB* total bilirubin

Table 3 Postoperative complications

Complications	OH ($n=307$)	LH ($n=41$)	P value
Patient numbers	66 (21.5%)	6 (14.6%)	0.416
Bile leakage	6 (2.0%)	1 (2.4%)	0.551
Liver failure	1 (0.3%)	0 (0.0%)	0.715
Ascites	29 (9.4%)	3 (4.9%)	0.776
Pulmonary infection	12 (3.9%)	1 (2.4%)	0.927
Pleural effusion	7 (2.3%)	0 (0.0%)	0.329
SSI	11 (3.6%)	1 (2.4%)	1.000
Clavien–Dindo classification			
Grade I–II	53	4	0.793
Grade III–IV	12	2	0.373
Grade V	1	0	0.763

OH open hepatectomy, *LH* laparoscopic hepatectomy, *SSI* surgical site infection

Table 4 Associations of surgical methods with overall survival and disease-free survival

	Non-adjusted	Adjusted[a]
Total		
Overall survival		
OH	1	1
LH	0.6 (0.2, 1.7) 0.374	0.6 (0.2, 2.3) 0.487
Disease-free survival		
OH	1	1
LH	0.5 (0.2, 1.1) 0.083	0.7 (0.3, 1.9) 0.550
Survival after PSM		
Overall survival		
OH	1	1
LH	2.7 (0.7, 10.1) 0.120	1.7 (0.4, 7.3) 0.473
Disease-free survival		
OH	1	1
LH	1.2 (0.5, 2.9) 0.757	0.4 (0.1, 1.2) 0.119

Data were presented as HR (95% CI) P value

OH open hepatectomy, *LH* laparoscopic hepatectomy, *PSM* propensity score matching

[a]These factors were adjusted: age; sex; HBsAg; classification; ALBI; MVI; major vascular tumor thrombus; tumor differentiation; tumor size and tumor number, blood loss, duration of operation and duration of vascular exclusion

clinical situations including evaluation of liver function before hepatectomy, evaluation of liver function in patients with liver failure, assessment of graft and donor function in liver transplantation and survival prediction after liver resection in patients with HCC [29–35]. In previous published studies, the ALBI grade has been proved to be a simple, objective, evidence-based and discriminatory method of evaluating liver function in patients with HCC [18, 36–39]. Compared to the Child–Pugh grade, ALBI grade does not include individual parameters (such as ascites and hepatic encephalopathy) that were scored according to empirically defined, predetermined cutoff points. In addition, the Child–Pugh grade failed to categorize patients into distinct groups. Consequently, in PSM

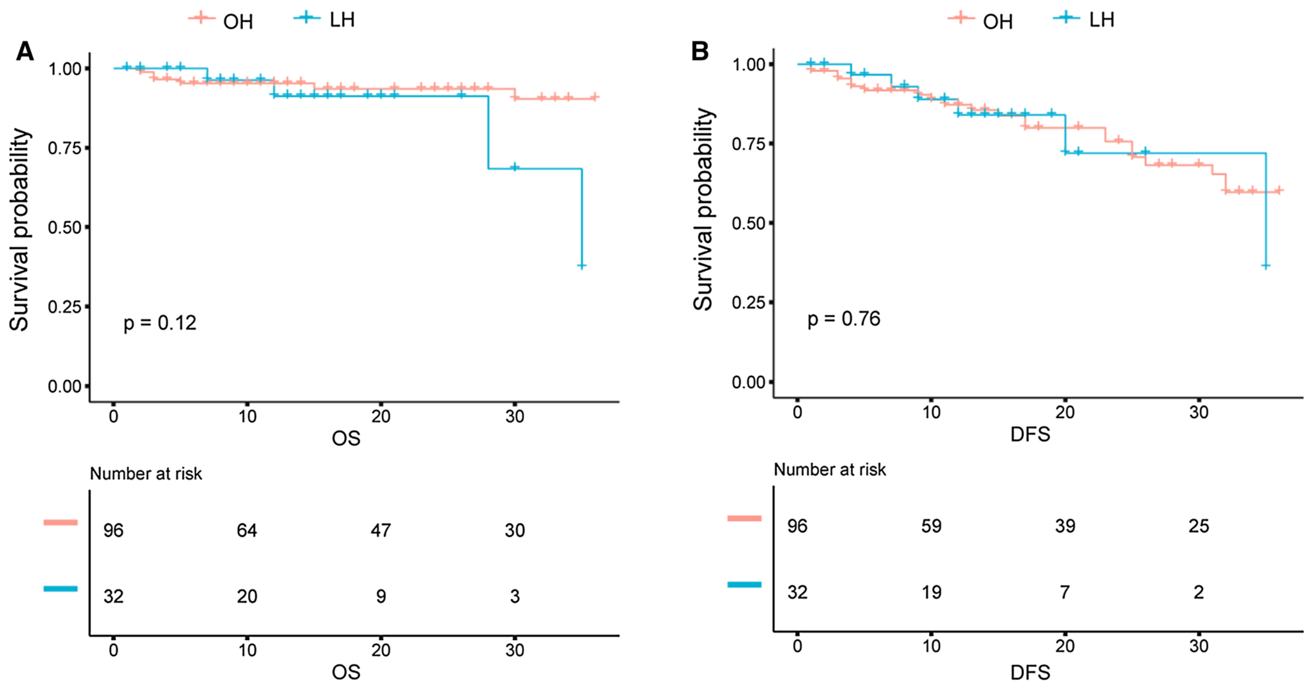

Fig. 4 Long-term survival outcomes after laparoscopic mesohepatectomy and open mesohepatectomy in propensity score matching population. **A** Overall survival rate; **B** disease-free survival rate

method, we matched liver function between two groups based on ALBI grade and ICG-R15.

In addition to preoperative liver quality, the prognosis after hepatectomy was also related to the location of tumors and extent of liver resection [19]. Therefore, one of the most important factors we matched was tumor classification. The classification for CL-HCC was established before and its value in guiding surgical treatment and prognosis prediction was validated in our previous study [19]. According to this classification, patients undergoing LM were predominately from type III and I. For type II patients, LM can also be carried out in selected patients with smaller tumor size and without direct vascular invasion. However, in type II, due to the difficult tumor location and its close proximity to vascular branches, LM in these patients were more challenging and it was more difficult to achieve tumor clearance or anatomic resection. In our experience, type IV patients and type II patients with a direct vascular invasion may be contraindications for LM in the present technical condition. After PSM, most of patients in LM group were classified into type III (78.1%). For patients in type III, tumors were located between segments IVa and VIII and segments V and IVb; thus, in some cases, segments IV, V and VIII should be resected to achieve anatomic resection [17]. In the present study, we excluded patients undergoing only one Couinaud's segment resection (such as segment V) owing to the heterogeneity in tumor parameters and surgical procedures.

In addition to liver function and tumor classification, other prognostic indicators including anatomic resection and several tumor biological parameters (MVI, differentiation and capsulation) were also matched in PSM method. Admittedly, it is more difficult to achieve anatomic resection in LM technique, especially for patients in type II, because the operative field is far from the conventional sites of abdominal trocar, and the liver poses a barrier to free movement of the laparoscopic instruments. However, we reported similar rates of anatomic resection in both groups before and after adjustment. In previous studies, non-anatomic resection has been demonstrated to be an independent risk factor for postoperative local tumor recurrence and tumor-specific survival for patients with HCC [21], thus anatomic resection rate should be an indicator of feasibility and efficacy of LM technique.

Previous reports showed that a reduced rate of PM was observed in the laparoscopic group [40, 41], due to the hemostatic effect of the pneumoperitoneum as well as the use of ultrasonic dissection devices. However, we found a longer vascular exclusion duration in patients undergoing LM. Actually, in the present study, PM was a routine procedure during liver parenchyma transection in LM group because most of patients in this study had liver cirrhosis and intraoperative bleeding control was more challenging in these patients. In our experience, benefits of PM (reduction of blood loss) may outweigh injuries caused by PM technique (e.g., ischemia–reperfusion injury). For some type II patients, except for PM, the infra- and supra-hepatic inferior vena cava were also exposed and encircled for probable exclusion because tumors had a close proximity to the vascular structures in the second porta hepatis. Additionally, hepatic venous outflow stenosis or obstruction after LM is an unusual but fatal complication, especially for patients with severe liver cirrhosis [42]. For type II patients, hepatic outflow should be protected carefully during LM procedures.

In the present study, no significant differences were observed in blood loss and intraoperative blood transfusion between two groups. In LM technique, we acquired a better visualization of vessels and high intra-abdominal pressure caused by pneumoperitoneum. In addition, we utilized series of blood control techniques and advanced instruments (e.g., linear stapler and electric coagulator). However, the present study did not demonstrate a significant reduction in blood loss in the LM group. Total duration of operation was also similar between two groups. Actually, time of liver parenchyma transection was longer in LM group because of the inherent more difficult procedures and more frequent application of PM in LM group. However, patients in LM group had shorter time for abdominal closure owing to the smaller surgical incisions. Decreased length of hospital stay has been shown to be a benefit of laparoscopic technique [5, 22]. Similarly, in the present study, LM was associated with a shorter hospital stay. This benefit was presumed to be associated with the observed decrease in the time to oral intake of nutrition and off-bed activity in LM group. Additionally, less postoperative morbidity rate was also related to the decreased length of hospital stay in LM group. In the current study, after PSM, the LM group had lower overall postoperative morbidity rate. It has been reported that laparoscopic hepatectomy decreased rates of postoperative complications such as infectious complications and intractable ascites [7, 26, 43–45]. In our study, the incidences of ascites, pulmonary infection and surgical site infection after LM were lower than the incidences after OM. However, the differences were not statistically significant. In addition, 90-day mortality rates were comparable between the groups.

Although the short-term benefits of laparoscopic hepatectomy in patients with HCC were well established in previous reports [5, 7, 8, 16], there is no consensus regarding the long-term benefits of this procedure. Cheung et al. demonstrated favorable long-term outcomes of laparoscopic hepatectomy in HCC patients [46]. The oncological benefit of the laparoscopic approach over the open approach can be explained by the reason that the anterior approach used in laparoscopic procedures needed less tissue manipulation, which reduces hematogenous spread of tumor cells during hepatectomy [47]. In contrast, previous meta-analyses have demonstrated comparable long-term outcomes in terms of OS and DFS between open and laparoscopic techniques [48–50]. However, this conclusion was not validated in those undergoing LM. For patients undergoing mesohepatectomy, our study showed that oncological prognosis was not altered by laparoscopy. No significant differences were observed in OS and DFS rates between the two matched groups. Additionally, multivariable analyses also did not find significantly long-term prognostic difference between two groups after adjusting potential confounding factors.

The current study carries some limitations related to its retrospective nature. First, the small sample size and absence of randomization may limit the strength and validity of the outcomes. Second, longer follow-up time is still needed to explore the long-term prognostic differences between two groups. Third, there can be other confounders and potential mediators that were not adjusted in the multivariable models or PSM method. The generalizability and applicability of the conclusion in the present study need to be validated in specialized high-volume centers. At least one randomized clinical trial is required to compare advantages and disadvantages of two techniques.

In conclusion, patients undergoing LM technique had similar long-term prognosis compared to those who underwent OM. For the superiority of LM procedures in some postoperative outcomes, LM can be recommended to be a reasonable method for patients with CL-HCC. However, before carrying out LM procedure, a comprehensive understanding of liver anatomy, basic learning of laparoscopic techniques in other abdominal surgeries, knowing well of different energy devices and abundant open hepatectomy experiences are necessary. LM for CL-HCC is more technically challenging and has a steeper learning curve that should be considered. Nevertheless, we believe that with the well-established standardized procedures and application of advanced instruments that the learning period could be decreased in the future.

Compliance with ethical standards

Disclosures Drs Wei Li, Jun Han, Guowei Xie, Yang Xiao, Ke Sun, Kefei Yuan, Hong Wu have no conflicts of interest or financial ties to disclose.

References

1. Wu CC, Ho WL, Chen JT, Tang CS, Yeh DC, Liu TJ, P'Eng FK (1999) Mesohepatectomy for centrally located hepatocellular carcinoma: an appraisal of a rare procedure. J Am Coll Surg 188:508–515
2. Scudamore CH, Buczkowski AK, Shayan H, Ho SG, Legiehn GM, Chung SW, Owen DA (2000) Mesohepatectomy. Am J Surg 179:356–360
3. Chen X, Li B, He W, Wei YG, Du ZG, Jiang L (2014) Mesohepatectomy versus extended hemihepatectomy for centrally located hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 13:264–270

4. Reich H, McGlynn F, DeCaprio J, Budin R (1991) Laparoscopic excision of benign liver lesions. Obstet Gynecol 78:956–958
5. Ciria R, Cherqui D, Geller DA, Briceno J, Wakabayashi G (2016) Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. Ann Surg 263:761–777
6. Chen J, Bai T, Zhang Y, Xie ZB, Wang XB, Wu FX, Li LQ (2015) The safety and efficacy of laparoscopic and open hepatectomy in hepatocellular carcinoma patients with liver cirrhosis: a systematic review. Int J Clin Exp Med 8:20679–20689
7. Franken C, Lau B, Putchakayala K, DiFronzo LA (2014) Comparison of short-term outcomes in laparoscopic vs open hepatectomy. JAMA Surg 149:941–946
8. Lee W, Han HS, Yoon YS, Cho JY, Choi Y, Shin HK, Jang JY, Choi H, Jang JS, Kwon SU (2016) Comparison of laparoscopic liver resection for hepatocellular carcinoma located in the posterosuperior segments or anterolateral segments: a case-matched analysis. Surgery 160:1219–1226
9. Yoon YI, Kim KH, Kang SH, Kim WJ, Shin MH, Lee SK, Jung DH, Park GC, Ahn CS, Moon DB, Ha TY, Song GW, Hwang S, Lee SG (2017) Pure laparoscopic versus open right hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score matched analysis. Ann Surg 265:856–863
10. Takahara T, Wakabayashi G, Konno H, Gotoh M, Yamaue H, Yanaga K, Fujimoto J, Kaneko H, Unno M, Endo I, Seto Y, Miyata H, Miyazaki M, Yamamoto M (2016) Comparison of laparoscopic major hepatectomy with propensity score matched open cases from the National Clinical Database in Japan. J Hepatobiliary Pancreat Sci 23:721–734
11. Buell JF, Cherqui D, Geller DA, O’Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D’Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espat J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttil R, Belghiti J, Strasberg S, Chari RS (2009) The international position on laparoscopic liver surgery: the Louisville statement, 2008. Ann Surg 250:825–830
12. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, Asbun H, O’Rourke N, Tanabe M, Koffron AJ, Tsung A, Soubrane O, Machado MA, Gayet B, Troisi RI, Pessaux P, Van Dam RM, Scatton O, Abu Hilal M, Belli G, Kwon CH, Edwin B, Choi GH, Aldrighetti LA, Cai X, Cleary S, Chen KH, Schon MR, Sugioka A, Tang CN, Herman P, Pekolj J, Chen XP, Dagher I, Jarnagin W, Yamamoto M, Strong R, Jagannath P, Lo CM, Clavien PA, Kokudo N, Barkun J, Strasberg SM (2015) Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 261:619–629
13. Gumbs AA, Gayet B (2008) Totally laparoscopic central hepatectomy. J Gastrointest Surg 12::1153
14. Yoon YS, Han HS, Cho JY, Ahn KS (2009) Totally laparoscopic central bisectionectomy for hepatocellular carcinoma. J Laparoendosc Adv Surg Tech A 19:653–656
15. Machado MA, Kalil AN (2011) Glissonian approach for laparoscopic mesohepatectomy. Surg Endosc 25:2020–2022
16. Conrad C, Ogiso S, Inoue Y, Shivathirthan N, Gayet B (2015) Laparoscopic parenchymal-sparing liver resection of lesions in the central segments: feasible, safe, and effective. Surg Endosc 29:2410–2417
17. Qiu J, Wu H, Bai Y, Xu Y, Zhou J, Yuan H, Chen S, He Z, Zeng Y (2013) Mesohepatectomy for centrally located liver tumours. Br J Surg 100:1620–1626
18. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, O’Beirne J, Fox R, Skowronska A, Palmer D, Yeo W, Mo F, Lai P, Inarrairaegui M, Chan SL, Sangro B, Miksad R, Tada T, Kumada T, Toyoda H (2015) Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 33:550–558
19. Qiu J, Chen S, Wu H, Du C (2016) The prognostic value of a classification system for centrally located liver tumors in the setting of hepatocellular carcinoma after mesohepatectomy. Surg Oncol 25:441–447
20. Li W, Li L, Minigalin D, Wu H (2018) Anatomic mesohepatectomy versus extended hepatectomy for patients with centrally located hepatocellular carcinoma. HPB 20:530–537
21. Shindoh J, Makuuchi M, Matsuyama Y, Mise Y, Arita J, Sakamoto Y, Hasegawa K, Kokudo N (2016) Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. J Hepatol 64:594–600
22. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
23. Parfitt JR, Marotta P, Alghamdi M, Wall W, Khakhar A, Suskin NG, Quan D, McAllister V, Ghent C, Levstik M, McLean C, Chakrabarti S, Garcia B, Driman DK (2007) Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. Liver Transplant 13:543–551
24. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Buchler MW, Weitz J (2011) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 149:713–724
25. Taguchi Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Kokuryo T, Wakai K, Nagino M (2014) The determination of bile leakage in complex hepatectomy based on the guidelines of the International Study Group of Liver Surgery. World J Surg 38:168–176
26. Fuks D, Cauchy F, Fteriche S, Nomi T, Schwarz L, Dokmak S, Scatton O, Fusco G, Belghiti J, Gayet B, Soubrane O (2016) Laparoscopy decreases pulmonary complications in patients undergoing major liver resection: a propensity score analysis. Ann Surg 263:353–361
27. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999) Guideline for prevention of surgical site infection, 1999. Centers for disease control and prevention (CDC) hospital infection control practices advisory committee. Am J Infect Control 27:97–132 (**quiz 133–134; discussion 196**)
28. Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, Hu N, Paterson JM, Targownik L, Turin TC, Udell JA, Ernst P (2016) A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 374:1145–1154
29. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim GS, Kim SJ, Paik SW (2014) Can the model for end-stage liver disease score replace the indocyanine green clearance test in the selection of right hemihepatectomy in Child-Pugh class A? Ann Surg Treat Res 86:122–129
30. Stenmark MH, Cao Y, Wang H, Jackson A, Ben-Josef E, Ten Haken RK, Lawrence TS, Feng M (2014) Estimating functional liver reserve following hepatic irradiation: adaptive normal tissue response models. Radiother Oncol 111:418–423
31. Song P, Inagaki Y, Wang Z, Hasegawa K, Sakamoto Y, Arita J, Tang W, Kokudo N (2015) High levels of gamma-glutamyl transferase and indocyanine green retention rate at 15 min as preoperative predictors of tumor recurrence in patients with hepatocellular carcinoma. Medicine 94:e810
32. Nanashima A, Abo T, Tobinaga S, Nonaka T, Fukuoka H, Hidaka S, Takeshita H, Sawai T, Yasutake T, Nagayasu T, Kudo T (2011) Prediction of indocyanine green retention rate at 15 minutes by

correlated liver function parameters before hepatectomy. J Surg Res 169:e119–e125
33. Tang T, Feng X, Yan J, Xia F, Li X, Ma K, Bie P (2014) Predictive value of indocyanine green retention rate with respect to complications of radiofrequency ablation in 878 patients with hepatocellular carcinoma. Int J Hyperth 30:402–407
34. Ariizumi S, Yamamoto M, Takasaki K (2009) Right hepatectomy for hepatocellular carcinoma in patients with an indocyanine green retention rate at 15 minutes of 10% or higher. Dig Surg 26:135–142
35. Yoon HI, Koom WS, Lee IJ, Jeong K, Chung Y, Kim JK, Lee KS, Han KH, Seong J (2012) The significance of ICG-R15 in predicting hepatic toxicity in patients receiving radiotherapy for hepatocellular carcinoma. Liver Int 32:1165–1171
36. Hiraoka A, Michitaka K, Kumada T, Kudo M (2017) ALBI score as a novel tool in staging and treatment planning for hepatocellular carcinoma: advantage of ALBI grade for universal assessment of hepatic function. Liver Cancer 6:377–379
37. Hiraoka A, Kumada T, Hirooka M, Tsuji K, Itobayashi E, Kariyama K, Ishikawa T, Tajiri K, Ochi H, Tada T, Toyoda H, Nouso K, Joko K, Kawasaki H, Hiasa Y (2018) A better method for assessment of hepatic function in hepatocellular carcinoma patients treated with radiofrequency ablation: usefulness of albumin-bilirubin grade. Hepatol Res 48:E61-e67
38. Michitaka K, Toyoda H, Lai PB, O'Beirne J, Chong CC, Berhane S, Reeves H, Manas D, Fox RP, Yeo W, Mo F, Chan AW, Tada T, Inarrairaegui M, Vogel A, Schweitzer N, Chan SL, Sangro B, Kumada T, Johnson PJ (2016) Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. Hepatol Res 114:744–750
39. Hiraoka A, Michitaka K, Kumada T, Izumi N, Kadoya M, Kokudo N, Kubo S, Matsuyama Y, Nakashima O, Sakamoto M, Takayama T, Kokudo T, Kashiwabara K, Kudo M (2017) Validation and potential of albumin-bilirubin grade and prognostication in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan: the need for a more detailed evaluation of hepatic function. Liver Cancer 6:325–336
40. Bagante F, Spolverato G, Strasberg SM, Gani F, Thompson V, Hall BL, Bentrem DJ, Pitt HA, Pawlik TM (2016) Minimally invasive vs. open hepatectomy: a comparative analysis of the national surgical quality improvement program database. J Gastrointest Surg 20:1608–1617
41. Yan Y, Cai X, Geller DA (2017) Laparoscopic liver resection: a review of current status. J Laparoendosc Adv Surg Tech A 27:481–486
42. Li W, Wu H, Han J (2016) Surgical outcomes of hepatocellular carcinoma invading hepatocaval confluence. Hepatobiliary Pancreat Dis Int 15:593–601
43. Xu HW, Liu F, Li HY, Wei YG (2018) Outcomes following laparoscopic versus open major hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score-matched analysis. Surg Endosc 32:712–719
44. Scuderi V, Barkhatov L, Montalti R, Ratti F, Cipriani F, Pardo F, Tranchart H, Dagher I, Rotellar F, Abu Hilal M, Edwin B, Vivarelli M, Aldrighetti L, Troisi RI (2017) Outcome after laparoscopic and open resections of posterosuperior segments of the liver. Br J Surg 104:751–759
45. El-Gendi A, El-Shafei M, El-Gendi S, Shawky A (2017) Laparoscopic versus open hepatic resection for solitary hepatocellular carcinoma less than 5 cm in cirrhotic patients: a randomized controlled study. J Laparoendosc Adv Surg Tech A 28:302–310
46. Cheung TT, Dai WC, Tsang SH, Chan AC, Chok KS, Chan SC, Lo CM (2016) Pure laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma in 110 patients with liver cirrhosis: a propensity analysis at a single center. Ann Surg 264:612–620
47. Hayashi N, Egami H, Kai M, Kurusu Y, Takano S, Ogawa M (1999) No-touch isolation technique reduces intraoperative shedding of tumor cells into the portal vein during resection of colorectal cancer. Surgery 125:369–374
48. Croome KP, Yamashita MH (2010) Laparoscopic vs open hepatic resection for benign and malignant tumors: an updated meta-analysis. Arch Surg 145:1109–1118
49. Yin Z, Fan X, Ye H, Yin D, Wang J (2013) Short- and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. Ann Surg Oncol 20:1203–1215
50. Morise Z, Ciria R, Cherqui D, Chen KH, Belli G, Wakabayashi G (2015) Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 22:342–352