

Laparoscopy versus Laparotomy for the Treatment of BCLC Stages 0 or A Hepatocellular Carcinoma Associated with or without Microvascular Invasion: A Multicenter, Propensity Score Matching Analysis

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Abstract

Purpose: To analyze the long-term prognoses of Barcelona Clinic Liver Cancer (BCLC) stages 0 or A hepatocellular carcinoma (HCC) patients associated with or without microvascular invasion (MVI) treated with laparoscopy versus laparotomy using propensity score matched analysis.

Methods: The clinicopathological data of HCC patients at BCLC stages 0 or A from 4 major medical centers were retrospectively reviewed, and sub-grouped in terms of the presence of MVI to explore the effect of MVI on the long-term surgical outcomes. Propensity score matching (PSM) analysis was used to build a matched group of HCC patients for comparison of follow-up indicators between the laparoscopy and laparotomy groups.

Results: 495 HCC patients at BCLC stages 0 or A were enrolled, including 243 in the laparoscopic group and 252 in the laparotomic group. Laparoscopic resection group had a shorter operative time, less blood loss, and lower frequencies of blood transfusion and postoperative complication rates. After PSM, the laparoscopic group had a significantly better overall survival (OS) and recurrence-free survival (RFS) than the laparotomic group. Subgroup analysis demonstrated OS and RFS of patients without MVI were also significantly improved in the laparoscopic group compared with the laparotomic group. However, no significant difference of OS and RFS between two groups was found in patients with MVI after PSM.

Conclusions: Pure laparoscopic hepatectomy for HCC patients at early stages can be performed safely with favorable short-term and long-term outcomes at high-volume liver cancer centers, regardless of the presence of MVI.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common primary malignancies worldwide. Currently, approximately 740,000 new cases of HCC are diagnosed per year with a five-year survival rate of less than 8.37%[1, 2]. Microvascular invasion (MVI), defined as small thrombi consisting of malignant tumor cells in the portal or hepatic venous systems, is an important histopathologic feature of HCC. The presence of MVI indicates the aggressive behavior of HCC and predicts bad prognosis and adverse outcomes after hepatectomy or transplantation[3].

To improve the long-term outcomes of HCC patients with MVI, it is reasonable to employ personalized treatment modalities for those patients. A series of studies have shown that surgical resection provides better oncologic outcomes compared with radiofrequency ablation for MVI patients[4–6]. Furthermore, the prognostic value of MVI in different Barcelona Clinic Liver Cancer (BCLC) staging classifications and in eight existing staging systems is various[7, 8]. In addition, anatomic liver resection and wide resection margins are able to provide a better long-term prognosis[9–13]. However, whether different surgical approaches (laparoscopic and open surgery) have a significant impact on the long-term outcome of HCC patients with MVI currently lacks evidence-based research.

Laparoscopy has unique advantages such as less trauma, less pain, faster postoperative recovery and smaller incisions[14]. Multiple meta-analyses have confirmed the safety and effectiveness of laparoscopic resection applied in HCC patients. Ahmed et al.[15] and Zhou et al.[16] reported that laparoscopic resection is superior to open resection in terms of its perioperative results, and does not compromise the oncological outcomes. It is demonstrated that there was no statistical difference in the radical resection rate between laparoscopic surgery and open resection of HCC[17], suggesting the emergence of the era of laparoscopic hepatectomy. However, the long-term outcomes of laparoscopy are still unknown in HCC patients with BCLC stages 0 or A. It is unclear whether laparoscopic surgery can bring similar advantages to HCC patients with MVI compared with laparotomy. The operative characteristics and survival rates such as postoperative overall survival (OS) and recurrence-free survival (RFS) in HCC patients with MVI who underwent different surgical methods need to be further explored.

Herein, we aimed to analyze and compare the long-term prognoses of HCC patients associated with or without MVI at BCLC stages 0 or A who were treated with laparoscopy or open hepatectomy using propensity score matching analysis. Besides, MVI was applied to subgroup the HCC patients, with the purpose to investigate the changes of selected indicators in different surgery subgroups.

Methods

Patient selection

A total of 1104 HCC patients receiving surgical treatment at four high-volume medical centers (the Eastern Hepatobiliary Surgery Hospital, Fujian Provincial Hospital, Changzhou People's Hospital, and Affiliated Tumor Hospital of Guangxi Medical University) from March 2015 to February 2018 were retrospectively recruited. This study was in accordance with the Declaration of Helsinki (as revised in 2008) and was approved by the Clinical Research Ethics Committee of the four respective institutes. Written informed consent for clinical research was obtained from all the patients prior to enrollment.

The diagnosis of HCC was based on the guidelines for Diagnosis and Treatment of Primary Hepatocellular Carcinoma issued by American Association for the Study of Liver Diseases (AASLD)[18]. Patients who met the criteria of BCLC staging system of 0 or A (ECOG performance status score is 0, single tumor or up to 3 tumors less than 3 cm, and Child-Pugh class A–B) were included[19]. The exclusion criteria were as follows: (I) multiple tumors; (II) major vascular (portal vein, hepatic vein or their branches) or bile duct invasion; (III) intrahepatic spread or distant metastatic lesions; (IV) had other concurrent malignant tumors or metastatic liver cancer; (V) be complicated with serious cardiovascular or cerebrovascular diseases; (VI) abnormal coagulation function; and (VII) patients who had the emergency operation due to traumatic or spontaneous tumor rupture.

MVI is defined as the presence of tumor thrombi within the microscopic vessels adjacent to HCC. The presence of MVI is related to early tumor recurrence and poor postoperative outcomes after liver resection

and transplantation[20]. Here, the histopathologic examination was performed to confirm the presence of MVI.

Surgical Procedure

The laparoscopic hepatectomy was performed as previously reported[21, 22]. Briefly, the patient was in a supine position with full exposure to the location of the tumor. A 10mm trocar was placed in the umbilical cord, and laparoscopy was performed to observe the location and size of the liver space-occupying lesion. If the lesion was in the left liver, the main operative site should be located 2cm below the costal margin of the midline of the left clavicle. If the lesion was in the right liver, the operative site should be located 2cm below the costal margin of the midline of the right clavicle. The ligaments around the liver were separated with an ultrasound knife to make the liver be fully exposed. The liver was pre-labeled with an ultrasound knife, and the cutting edge should be more than 2 cm away from the tumor by LigaSure. The resected tumor specimens were placed in a collection bag. The incision needed hemostasis, and the abdominal cavity drainage tube was placed.

The open resection was conducted traditionally[23]. Briefly, the patient was in a supine position and the scope of resection was depended on tumor size and residual liver volume. General abdominal evaluation was carried out to exclude the metastasis, and liver evaluation was done to determine tumor's location, proximity to vessels, and to exclude multiplicity of tumors by manual palpation and intraoperative ultrasound. Parenchymal transection was performed using Cavitron ultrasonic surgical aspirator, LigaSure and bipolar forceps. Fibrin glue sealant was applied to seal the incision surface of the liver.

Follow-up

All patients were followed up every two months in the first year after discharge, and every three months thereafter. Follow-up examinations were conducted using laboratory findings (white blood cell count, hemoglobin, platelets count, serum total bilirubin, albumin (ALB), aspartate aminotransferase (AST), glucose, creatinine, alpha-fetoprotein (AFP), prothrombin time (PT)), abdominal ultrasonography, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). After surgery, the patients were followed up every 3 to 4 months until death or dropout from the follow-up program. A diagnosis of recurrence of HCC was based on CT and/or MRI and elevated serum AFP levels.

Statistical analysis

Statistical evaluation was performed using SPSS software (IBM SPSS Statistics 21; SPSS Inc., Chicago, IL). Continuous variables with a normal distribution were presented as mean \pm standard deviation (SD); continuous variables with skewed distribution were expressed as median (range). Propensity score matching (PSM) analysis was performed using all the baseline covariates to minimize the selection bias, including age, sex, body mass index (BMI), hepatitis B infection, antiviral treatment, hypertension,

diabetes, liver cirrhosis, tumor diameter, MVI, resection margin involvement, white blood cell (WBC) count, hemoglobin, platelet count, serum total bilirubin, ALB, AST, glucose, creatinine, AFP and PT.

For the two-group comparison, *t*-test was applied for continuous variables meeting normal distribution, and Mann-Whitney U test was used for continuous variables with skewed distribution. Chi-square test or Fisher's exact test was used for categorical variables as appropriate. The Kaplan-Meier method and log-rank test were used for survival analyses.

Univariate and multivariate Cox regression analyses were conducted by COXPH function of survival package from R language (version 3.6.3). Parameters with P values less than 0.05 in the univariate regression analysis were further incorporated into multivariate analysis, and independent prognostic factors were screened out by regressive log-likelihood ratio test. Probability values (P) <0.05 were considered to be statistically significant.

Results

Baseline characteristics

A total of 1104 HCC patients were collected in this study. Among them, 495 patients (aged from 18 to 70) were at BCLC stages 0 or A, 478 patients were at stage B, and 131 patients were at stage C. In this study, 495 HCC patients with BCLC stages 0 or A, including 243 patients who received laparoscopy and 252 who underwent laparotomy, were eventually enrolled and analyzed (Figure 1). After PSM, 189 patients who received laparoscopy and 189 who underwent laparotomy were included. The baseline clinicopathological characteristics of HCC patients before and after PSM are shown in Table 1. After PSM, the statistically significantly different parameters, such as diabetes, tumor diameter, presence of MVI, surgical margin involvement, WBC count, AST and PT, became comparable between the laparoscopic and laparotomic groups (all $P \geq 0.05$) (Table 1).

Table 1
Baseline characteristics of patients before and after PSM

Characteristics	Before PSM		P-value	After PSM		P-value
	Laparoscopy (n= 243)	laparotomy (n = 252)		laparoscopy (n= 189)	Laparotomy (n = 189)	
Age (year)	59.0 [50.0;66.0]	60.0 [51.0;68.0]	0.347	59.0 [50.0;66.0]	59.0 [50.0;66.0]	0.965
Sex, male (%)	202 (83.1%)	217 (86.1%)	0.426	159 (84.1%)	162 (85.7%)	0.774
BMI	22.9 [20.9;25.0]	22.3 [20.3;24.8]	0.144	22.8 [20.9;24.9]	22.5 [20.3;25.0]	0.524
Hepatitis B infection (%)	188 (77.4%)	208 (82.5%)	0.185	154 (81.5%)	157 (83.1%)	0.788
Antiviral (%)	75 (30.9%)	61 (24.2%)	0.119	50 (26.5%)	50 (26.5%)	1.000
Hypertension (%)	53 (21.8%)	70 (27.8%)	0.152	44 (23.3%)	51 (27.0%)	0.477
Diabetes (%)	39 (16.0%)	61 (24.2%)	0.032	35 (18.5%)	44 (23.3%)	0.312
Liver cirrhosis (%)	175 (72.0%)	169 (67.1%)	0.272	133 (70.4%)	132 (69.8%)	1.000
Tumor diameter (cm)			<0.001			0.536
≤ 5	141 (58.0%)	96 (38.1%)		90 (47.6%)	83 (43.9%)	
>5	102 (42.0%)	156 (61.9%)		99 (52.4%)	106 (56.1%)	
MVI			0.024			0.916
Negative	132 (54.3%)	163 (64.7%)		115 (60.8%)	117 (61.9%)	
Positive	111 (45.7%)	89 (35.3%)		74 (39.2%)	72 (38.1%)	
Resection margin			0.017			1.000
Wide	95 (39.1%)	72 (28.6%)		59 (31.2%)	58 (30.7%)	
Narrow	148 (60.9%)	180 (71.4%)		130 (68.8%)	131 (69.3%)	
White blood cell count, ×10 ⁹ /L			0.034			0.179

PSM, propensity score matching; BMI, body mass index; MVI, microvascular invasion; ALB, albumin; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; PT, prothrombin time

Characteristics	Before PSM			After PSM		
	Laparoscopy (n= 243)	laparotomy (n = 252)	P- value	laparoscopy (n= 189)	Laparotomy (n = 189)	P- value
≤ 4	23 (9.47%)	41 (16.3%)		21 (11.1%)	31 (16.4%)	
>4	220 (90.5%)	211 (83.7%)		168 (88.9%)	158 (83.6%)	
Hemoglobin, g/L,			0.290			0.620
≤ 100	7 (2.88%)	13 (5.16%)		7 (3.70%)	10 (5.29%)	
>100	236 (97.1%)	239 (94.8%)		182 (96.3%)	179 (94.7%)	
Platelet count, ×10 ⁹ /L			0.552			0.392
≤ 100	23 (9.47%)	29 (11.5%)		16 (8.47%)	22 (11.6%)	
>100	220 (90.5%)	223 (88.5%)		173 (91.5%)	167 (88.4%)	
Serum total bilirubin, umol/L			0.599			1.000
≤ 17.5	190 (78.2%)	191 (75.8%)		146 (77.2%)	146 (77.2%)	
> 17.5	53 (21.8%)	61 (24.2%)		43 (22.8%)	43 (22.8%)	
ALB (g/L)			0.893			1.000
≤ 35	25 (10.3%)	24 (9.52%)		17 (8.99%)	18 (9.52%)	
>35	218 (89.7%)	228 (90.5%)		172 (91.0%)	171 (90.5%)	
AST (U/L)			0.010			0.502
≤ 45	183 (75.3%)	162 (64.3%)		135 (71.4%)	128 (67.7%)	
≥45	60 (24.7%)	90 (35.7%)		54 (28.6%)	61 (32.3%)	
Glucose, mmol/L			0.485			0.321
≤ 7	218 (89.7%)	220 (87.3%)		172 (91.0%)	165 (87.3%)	
>7	25 (10.3%)	32 (12.7%)		17 (8.99%)	24 (12.7%)	

PSM, propensity score matching; BMI, body mass index; MVI, microvascular invasion; ALB, albumin; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; PT, prothrombin time

Characteristics	Before PSM			After PSM		
	Laparoscopy (n= 243)	laparotomy (n = 252)	P- value	laparoscopy (n= 189)	Laparotomy (n = 189)	P- value
Creatinine, umol/L			0.722			1.000
≤ 106	236 (97.1%)	247 (98.0%)		184 (97.4%)	185 (97.9%)	
>106	7 (2.88%)	5 (1.98%)		5 (2.65%)	4 (2.12%)	
AFP (ng/ml)			0.143			0.587
≤ 400	174 (71.6%)	164 (65.1%)		128 (67.7%)	122 (64.6%)	
> 400	69 (28.4%)	88 (34.9%)		61 (32.3%)	67 (35.4%)	
PT(s)			0.007			0.622
≤ 13.5	197 (81.1%)	177 (70.2%)		149 (78.8%)	144 (76.2%)	
> 13.5	46 (18.9%)	75 (29.8%)		40 (21.2%)	45 (23.8%)	
PSM, propensity score matching; BMI, body mass index; MVI, microvascular invasion; ALB, albumin; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; PT, prothrombin time						

Survival analyses in HCC patients treated by laparoscopy or laparotomy before and after PSM

Before PSM, in the laparoscopic group, the OS at 1, 2, 3 and 5 years were 93.7%, 85.9%, 82.6% and 78.8%, respectively, and the RFS at 1, 2, 3 and 5 years were 81%, 77.7%, 75% and 71.4%, respectively. As for patients in the laparotomic group, the OS at 1, 2, 3 and 5 years were 88.1%, 77.3%, 67.9% and 55.7%, respectively, and the RFS at 1, 2, 3 and 5 years were 72.8%, 66.1%, 58.7% and 53.6%, respectively. The results indicated that the OS and RFS were significantly better in the laparoscopic group compared with the laparotomic group (both $P < 0.001$) (Figure 2A-B).

After PSM, in the laparoscopic group, the OS at 1, 2, 3 and 5 years were 93.0%, 84.4%, 80.3% and 75.8%, respectively, and the RFS at 1, 2, 3 and 5 years were 80.5%, 76.9%, 73.4% and 70.9%, respectively. In the laparotomic group, the OS at 1, 2, 3 and 5 years were 89.9%, 78.9%, 70.9% and 61%, respectively, and the RFS at 1, 2, 3 and 5 years were 73.8%, 68.2%, 62% and 56.8%, respectively. The results after PSM still showed a better OS and RFS in the laparoscopic group compared with the laparotomic group (both $P < 0.05$) (Figure 2C-D).

Subgroup analyses in HCC patients with MVI treated with laparoscopy or laparotomy before and after PSM

As shown in Figure 3, before PSM, both OS and RFS of MVI negative patients were significantly better in the laparoscopic group compared with the laparotomic group (both $P < 0.001$) (Figure 3A-B). The OS and RFS of MVI positive patients were also significantly improved in the laparoscopic group compared with the laparotomic group (both $P < 0.05$) (Figure 3C-D). After PSM, the OS and RFS of MVI negative patients were also significantly better in the laparoscopic group compared with the laparotomic group (both $P < 0.05$) (Figure 4A-B). However, no significant difference for OS and RFS was observed in MVI positive patients in the laparoscopic and laparotomic groups after PSM (Figure 4C-D).

Independent risk factors for OS and RFS in HCC patients before and after PSM

Before PSM, HBV infection, diabetes, abnormal level of AST and AFP, tumor size > 5 cm, the presence of MVI, and open resection approach were independent predictive factors of OS. As for RFS, multivariate analyses demonstrated that diabetes, abnormal levels of AST, TBIL and AFP, tumor size > 5 cm, the presence of MVI, and open resection approach were the independent risk factors (all $P < 0.05$) (Table 2).

After PSM, as presented in Table 3, multivariate analyses identified that the history of HBV infection and the absence of antiviral therapy were the independent risk factors of OS. Besides, it was identified that abnormal levels of AST, tumor diameter > 5 cm, MVI and open resection method were the independent risk factors for both OS and RFS (all $P < 0.05$).

Table 3

Univariate and multivariate analysis of overall survival and recurrence-free survival for patients after PSM

Table 2 Univariate and multivariate analysis of OS and RFS for patients before PSM								
Characteristics	OS				RFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P-value	HR	95%CI	P-value	P-value	HR	95%CI	P-value
Age (year)	0.700				0.700	0.71	(0.44-1.16)	0.174
Sex (male vs female)	0.900				0.800			
HBV	0.003	2.43	(1.36-4.35)	0.003	0.078			
Antiviral (yes vs no)	0.053				0.400			
Hypertension (yes vs no)	0.044				0.110			
Diabetes (yes vs no)	0.010	1.66	(1.15-2.41)	0.007	0.021	1.55	(1.10-2.18)	0.013
WBC (≤ 4 vs >4) ($\times 10^9/L$)	>0.9				0.600			
HGB (≤ 100 vs >100) ($\times 10^9/L$)	0.084				0.400			
PT (≤ 13.5 vs >13.5) (sec)	0.026				0.100			
PLT (≤ 100 vs >100) ($\times 10^9/L$)	>0.9				0.500			
ALB (≤ 35 vs >35) ($\times 10^9/L$)	0.010				0.130			
AST (≤ 45 vs >45) ($\times 10^9/L$)	<0.001	1.57	(1.10-2.25)	0.013	<0.001	1.54	(1.11-2.13)	0.010
Glu (≤ 7 vs >7) ($\times 10^9/L$)	0.130				0.400			
Cr (≤ 106 vs >106) ($\times 10^9/L$)	>0.9				0.300			

Table 2 Univariate and multivariate analysis of OS and RFS for patients before PSM

TBIL (≤ 17.5 vs >17.5) (umol/L)	0.049	1.40	(0.97-2.03)	0.074	0.027	1.44	(1.03-2.01)	0.033
Cirrhosis (yes vs no)	0.900				0.600			
AFP (≤ 400 vs >400) (umol/L)	<0.001	1.53	(1.08-2.17)	0.016	<0.001	1.42	(1.03-1.95)	0.031
Tumor (>5 vs ≤ 5) (cm)	<0.001	2.44	(1.63-3.65)	<0.001	<0.001	1.84	(1.31-2.60)	<0.001
Margin (>1 vs ≤ 1) (cm)	0.500				0.500			
MVI (positive vs negative)	0.019	1.46	(1.02-2.10)	0.041	0.003	1.41	(1.03-1.95)	0.034
Operative type (lap vs open)	<0.001	1.58	(1.08-2.30)	0.018	<0.001	1.46	(1.06-2.02)	0.021

PSM, propensity score matching; OS, overall survival; RFS, recurrent-free survival; CI, confidence interval; HBV, hepatitis B virus; WBC, white blood cells; HGB, hemoglobin; PT, prothrombin time; PLT, platelets; ALB, albumin; AST, aspartate aminotransferase; Glu, glucose; Cr, creatinine; TBIL, serum total bilirubin; AFP, alpha-fetoprotein; MVI, microvascular invasion

Characteristics	OS				RFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P-value	HR	95%CI	P-value	P-value	HR	95%CI	P-value
Age (year)	>0.9				>0.9			
Sex (male vs female)	0.600				0.200			
HBV	0.011	2.25	(1.25-4.07)	0.007	0.300			
Antiviral (yes vs no)	0.010	1.53	(1.05-2.22)	0.026	0.200			
Hypertension (yes vs no)	0.200				0.200			
Diabetes (yes vs no)	0.094				0.110			
WBC (≤ 4 vs >4) ($\times 10^9/L$)	0.800				0.500			
HGB (≤ 100 vs >100) ($\times 10^9/L$)	0.200				0.700			
PT (≤ 13.5 vs >13.5) (sec)	0.500				0.800			
PLT (≤ 100 vs >100) ($\times 10^9/L$)	0.800				0.800			
ALB (≤ 35 vs >35) ($\times 10^9/L$)	0.011				0.032			
AST (≤ 45 vs >45) ($\times 10^9/L$)	<0.001	1.70	(1.20-2.42)	0.003	<0.001	1.61	(1.17-2.22)	0.004
Glu (≤ 7 vs >7) ($\times 10^9/L$)	0.200				0.400			
Cr ($\leq 10^6$ vs $>10^6$) ($\times 10^9/L$)	>0.9				0.600			

PSM, propensity score matching; OS, overall survival; RFS, recurrent-free survival; CI, confidence interval; HBV, hepatitis B virus; WBC, white blood cells; HGB, hemoglobin; PT, prothrombin time; PLT, platelets; ALB, albumin; AST, aspartate aminotransferase; Glu, glucose; Cr, creatinine; TBIL, serum total bilirubin; AFP, alpha-fetoprotein; MVI, microvascular invasion

Characteristics	OS				RFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P-value	HR	95%CI	P-value	P-value	HR	95%CI	P-value
TBIL (≤ 17.5 vs >17.5) (umol/L)	0.200				0.200			
Cirrhosis (yes vs no)	0.700				0.500			
AFP (≤ 400 vs >400) (umol/L)	0.008				0.021			
Tumor (>5 vs ≤ 5) (cm)	<0.001	2.63	(1.77-3.91)	<0.001	<0.001	1.91	(1.37-2.68)	<0.001
Margin (>1 vs ≤ 1) (cm)	0.700				0.600			
MVI (positive vs negative)	0.005	1.45	(1.02-2.07)	0.041	0.002	1.41	(1.03-1.92)	0.033
Operative type (lap vs open)	0.014	1.81	(1.24-2.65)	0.002	0.014	1.55	(1.12-2.13)	0.008
PSM, propensity score matching; OS, overall survival; RFS, recurrent-free survival; CI, confidence interval; HBV, hepatitis B virus; WBC, white blood cells; HGB, hemoglobin; PT, prothrombin time; PLT, platelets; ALB, albumin; AST, aspartate aminotransferase; Glu, glucose; Cr, creatinine; TBIL, serum total bilirubin; AFP, alpha-fetoprotein; MVI, microvascular invasion								

Intraoperative And Postoperative Parameters Of Hcc Patients

The median operative time (160 min vs 180 min, $P<0.05$), median blood loss (200 ml vs 300 ml, $P<0.001$) and the frequency of blood transfusion (8.64% vs 20.2%, $P<0.001$) were significantly lower in the laparoscopic group than the laparotomic group (Table S1). However, the laparoscopic hepatectomy was more likely to require the vascular inflow occlusion (Pringle's maneuver) (30% vs 17.5%, $P=0.001$) compared with the laparotomic liver resection. The postoperative complication rates were analyzed as well. As shown in Table 2, the rates of hydrothorax and ascites were significantly lower in the laparoscopic group than the laparotomic group (2.06% vs 7.14%, $P<0.05$; 2.06% vs 10.3%, $P<0.001$, respectively). The rates of other complications, such as hepatic failure and bile leakage, were comparable in the two groups.

Discussion

In this study, the PSM analysis was used to construct a matched group of HCC patients for comparison of follow-up indicators including laboratory examination and operation features between the laparoscopic and open hepatectomy groups to minimize selection biases. The results showed that the OS and RFS of patients without MVI were significantly improved in the laparoscopic group than the laparotomic group before and after PSM. The OS and RFS of patients with MVI were also remarkably increased in the laparoscopic group compared with the laparotomic group before PSM; and the OS and RFS of patients with MVI were equivalent between the laparoscopic and laparotomic groups after PSM. Thus, laparoscopic hepatectomy can be considered as a feasible alternative in HCC patients at BCLC stages 0 or A regardless of the presence of MVI.

Also, operative outcomes of laparoscopy and laparotomy were analyzed in this study. It was shown that laparoscopic hepatectomy had a shorter operative time, less blood loss and lower frequency of blood transfusion; and the recurrence and mortality rates were also decreased in the laparoscopic group. We speculated the higher efficacy and less need for blood transfusion of laparoscopic hepatectomy may be associated with the small incision and less surgical trauma. A previous study demonstrated that laparoscopic right hepatectomy was associated with a tendency of prolonged operative time and less intraoperative blood loss after PSM[24]. We speculated that the prolonged operative time may be related to the relatively difficult operation technique and the limited vision field of the right hepatectomy. Toru et al.[25] reported that the median estimated blood loss and median postoperative hospital stay were significantly reduced in the laparoscopic group, but the laparoscopic and laparotomic groups had similar morbidity and mortality rates. Additionally, the postoperative complication rates were also analyzed in the present study. We found that the rates of hydrothorax and ascites were significantly lower in the laparoscopic group compared to the laparotomic group, because the laparoscopy is less traumatic than laparotomy. However, a previous study reported that postoperative complication rates were comparable between the two groups in the PSM cohort[25]. Hence, the operative time, the safety degree and prognosis of these two operation approaches are still controversial. The different outcomes in these studies can be affected by the skill and experience of operators.

Burgeoning literature compared the impact of laparoscopic and laparotomic hepatectomy on patients' survival. A meta-analysis in 2013 including 1238 patients from 15 studies indicated that the laparoscopic group may have short-term advantages in terms of blood loss and postoperative morbidity for HCC, but both procedures have similar long-term outcomes[26]. Another meta-analysis in 2018 showed that laparoscopic hepatectomy was associated with significantly lower tumor recurrence; the laparoscopic group conferred greater overall survival at 1- and 5-years [27]. No significant difference was found in long-term outcomes between the laparoscopic and laparotomic groups in early years, and the possible reasons caused this phenomenon may be as follows: (1) Laparoscopic technology was not mature at that time; (2) The indication of laparoscopy was primarily limited to minor hepatectomy; few major hepatectomy operations were performed using laparoscopy; (3) No advanced assisting technologies, such as intraoperative ultrasound and immunofluorescence, were applied during operations.

The presence of MVI worsens survival outcomes of HCC postoperatively, an accurate preoperative prediction of MVI can help surgeons to better choose surgical procedures[28]. Nevertheless, it is elusive whether MVI can provide prognostic information for patients at a specific tumor stage. Many efforts have been made to preoperatively estimate the presence of MVI. Some studies reported that some types of MVI are shown as the “typical dynamical pattern” on contrast-enhanced MRI[29, 30]; while other studies recommended the detection of serum tumor biomarkers to evaluate MVI[31]. However, the clinical practicability of these methods in the preoperative risk estimation of MVI remains to be confirmed.

Cheng et al.[7] documented that the occurrence rates of MVI at BCLC stages 0, A, and B were 12.4%, 26.2%, and 34.4%, respectively. Besides, they found MVI was an independent risk factor for OS and RFS in patients at BCLC stage A. Wang et al[32]. showed MVI could predict an adverse recurrence pattern and poor prognosis and had the potential to be used as a reference index when deciding whether to operate. In line with the previous studies, we also confirmed worse survival outcomes in HCC patients with MVI.

Besides, our study demonstrated that the long-term prognosis of patients without MVI who underwent laparoscopic resection were significantly better than that of patients without MVI who received open resection before and after PSM. We speculated that loss of blood, length of hospitalization and postoperative complications were potential factors which influenced patients’ survival [33–36]. On the other hand, patients diagnosed with MVI who underwent laparoscopic resection had similar long-term survival compared with patients associated with MVI who were treated with open resection before and after PSM. We hypothesized that the survival benefits of patients who underwent laparoscopic resection were counteracted by the presence of MVI. Thus, from a conservative viewpoint, our results can be interpreted to indicate that laparoscopy is at least not inferior to the standard open resection approach for HCC patients at BCLC stages 0 or A associated with MVI or not.

The present study has several limitations. First, this is a retrospective study with its inherent selection bias. Further prospective research needs to be designed and conducted. Next, although the number of patients enrolled in our study is relatively large, the sample size is still insufficient to draw a firm conclusion about the effect of MVI on the surgical choice in HCC patients. Last, this study was conducted in China with most patients having a background of HBV infection, whether the results of this study can be extrapolated to other different races and etiologies requires more studies.

Conclusion

Taken together, our study elucidated that for HCC patients at BCLC stages 0 or A, the long-term outcomes of patients who were treated with laparoscopic approach were at least not inferior to those of patients who underwent laparotomy approach. Therefore, laparoscopic liver resection may be a safe and feasible alternative for HCC patients at early stages, regardless of the presence of MVI.

Declarations

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Animal Research (Ethics)

Not applicable.

Ethics Approval and Consent to Participate (Ethics)

All procedures performed in this study involving human participants were approved by the Institutional Ethics Review Board of the Eastern Hepatobiliary Surgery Hospital, Fujian Provincial Hospital, The Third Affiliated Hospital of Soochow University, and Affiliated Tumor Hospital of Guangxi Medical University. This study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent for study participation was obtained from all the patients.

Consent to Publish (Ethics)

All authors confirm that the work described has not been published before and is not under consideration for publication elsewhere. All authors have seen and gave consent to the publication of this study. The publication of this work has been approved by the responsible authorities at the institution where the work is carried out.

Clinical Trials Registration

Not applicable because this is a retrospective observational study.

Conflict of Interest:

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Synopsis:

For hepatocellular carcinoma (HCC) patients at BCLC stage 0–A with or without microvascular invasion (MVI), laparoscopic liver resection may be a safe and feasible alternative for laparotomic liver resection.

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Figures

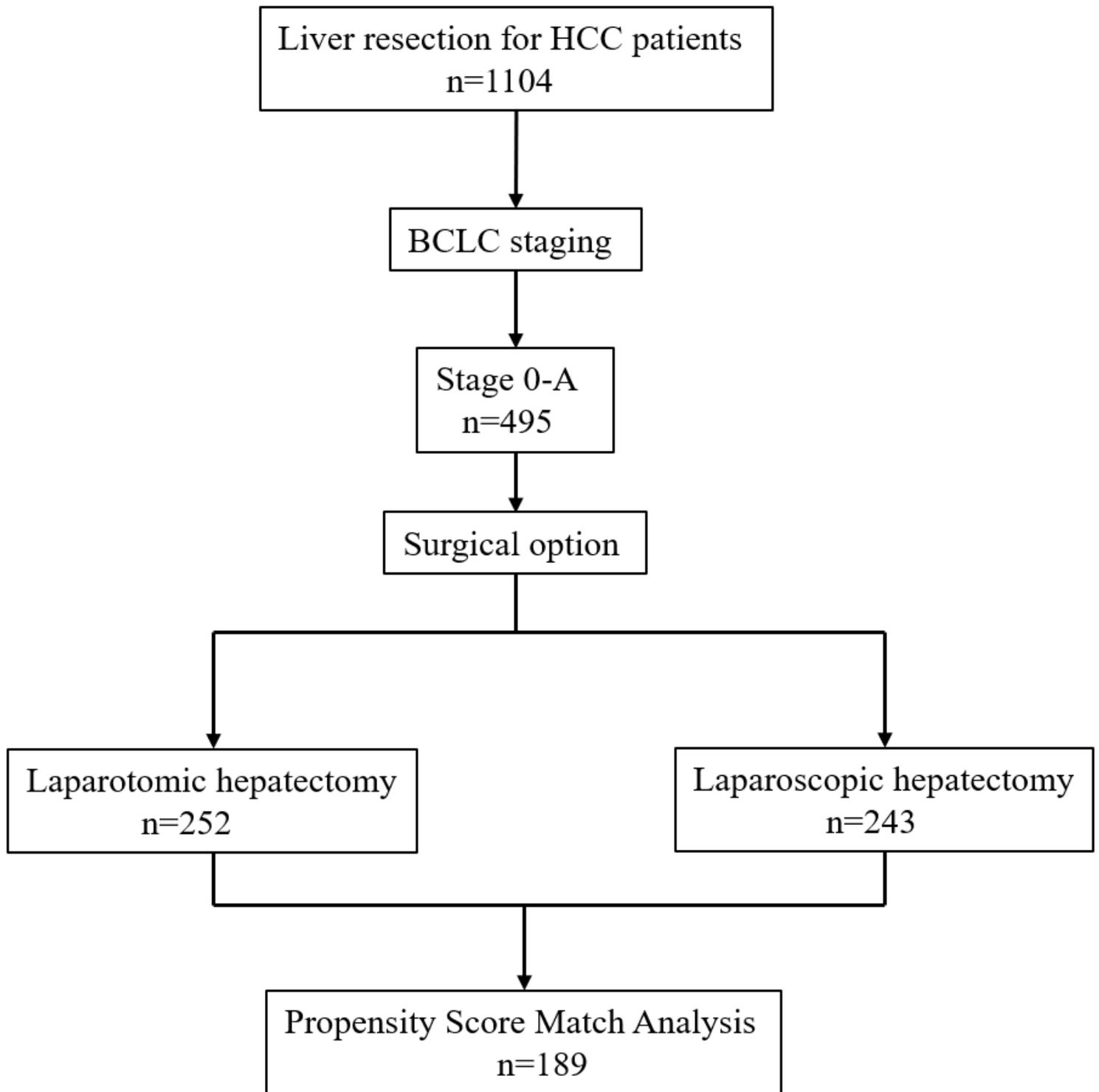


Figure 1

Study design frame, patient selection, and propensity score matching. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer

Figure 2

Overall survival (OS) and recurrence-free survival (RFS) of BCLC stages 0–A HCC patients treated with laparoscopy or laparotomy before and after PSM. OS (A) and RFS (B) of HCC patients at BCLC stages 0–A before PSM. OS (C) and RFS (D) of HCC patients at BCLC stages 0–A after PSM.

Figure 3

Overall survival (OS) and recurrence-free survival (RFS) of BCLC stages 0–A HCC patients with or without microvascular invasion (MVI) treated with laparoscopy or laparotomy before PSM. OS (A) and RFS (B) of HCC patients at BCLC stages 0–A without MVI before PSM. OS (C) and RFS (D) of HCC patients at BCLC stages 0–A with MVI before PSM.

Figure 4

Overall survival (OS) and recurrence-free survival (RFS) of BCLC stages 0–A HCC patients with or without microvascular invasion (MVI) treated with laparoscopy or laparotomy after PSM. OS (A) and RFS (B) of HCC patients at BCLC stages 0–A without MVI after PSM. OS (C) and RFS (D) of HCC patients at BCLC stages 0–A with MVI after PSM.

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