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ORIGINAL RESEARCH

Comparisons of Percutaneous Ablation, Open or Laparoscopic Liver Resection for Barcelona Clinic Liver Cancer Stage 0-A Hepatocellular Carcinoma: A Concurrent Generalized Propensity Score Analysis

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Purpose: Liver resection and ablation remain the most common therapeutic options for Barcelona Clinic Liver Cancer (BCLC) stage 0-A hepatocellular carcinoma (HCC), but there is a lack of evidence to show which is the most suitable therapy. This study aimed to make concurrent multi-arm comparisons of the short-term and long-term outcomes of percutaneous ablation (PA), open (OLR) or laparoscopic liver resection (LLR) for these patients.

Patients and Methods: This was a retrospective observational cohort study. A series of generalized propensity score methods for multiple treatment groups were performed to concurrently compare the clinical outcomes of these three treatment options to balance potential confounders. Regression standardization was used to account for hazard of all-cause mortality and recurrence of intergroup differences.

Results: Of the 1778 patients included, 1237, 307 and 234 underwent OLR, LLR and PA, respectively. After overlap weighting, which was the optimal adjustment strategy, patients in the minimally invasive group (LLR and PA groups) had few postoperative complications and short postoperative hospital stays (both $P < 0.001$). The 5-year recurrence-free survival (RFS) rate and 5-year overall survival (OS) rate were significantly higher in the LLR group when compared with the OLR and PA groups (RFS: 55.6% vs 48.0% vs 30.2%, $P < 0.001$; OS: 89.1% vs 79.7% vs 84.0%, $P = 0.020$). Multivariable Cox analysis and regression standardization showed that LLR was an independent factor for better RFS when compared with OLR and PA. In subgroup analysis, the long-term outcomes of patients with BCLC stage A HCC were consistent with the whole population.

Conclusion: In the observational study using various covariate adjustment analysis with excellent balance, LLR is not only minimally invasive, but also provides better RFS and equivalent OS for patients with BCLC stage 0-A HCC when compared with OLR and PA.

Keywords: hepatocellular carcinoma, laparoscopic liver resection, generalized propensity score analysis, overlap weighting, clinical outcome

Introduction

Primary liver cancer ranks as the seventh most common cancers and the second-leading cause of cancer-related mortality all over the world.[1] Hepatocellular carcinoma (HCC) accounts for more than 80% of primary liver cancers.[2] Due to advances in surveillance technology and popularization of screening programs in patients with high risks of HCC, an increasing number of patients with HCC are diagnosed in the early stage.[3] According to the Barcelona Clinic Liver Cancer (BCLC) strategy for treatment recommendation, liver resection, ablation and transplantation are the recommended treatment modalities for HCC

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in the very early stage (BCLC stage 0) and early stage (BCLC stage A).[4] Of note, liver transplantation is not commonly used because of organ shortage.[5] Therefore, liver resection and ablation remain the most common options for BCLC stage 0-A HCC. Currently, laparoscopic liver resection (LLR) has become more and more popular with many surgeons owing to its safety and minimal invasiveness, although open liver resection (OLR) is still considered as the gold standard operation to treat HCC.[6] The efficacy of OLR, LLR and percutaneous ablation (PA) for HCC patients is worthy of further discussion.

Currently, a growing number of randomized controlled trials (RCTs) have investigated clinical outcomes of OLR, LLR or PA for HCC patients. PA has shown comparable long-term outcomes to liver resection in early-stage or small HCC patients,[7–10] although one trial favored OLR for better overall survival (OS) and recurrence-free survival (RFS) for HCC meeting Milan criteria.[11] LLR has demonstrated similar long-term outcomes to OLR, with superior short-term results for solitary HCC less than 5 cm in cirrhotic patients,[12] although direct RCT comparisons with PA are currently lacking.

Given the accumulation of substantial observational data over the years, an increasing number of cohort studies have investigated the efficacy of OLR, LLR or PA for HCC patients. Observational cohort studies generally indicate that surgical resection provides longer RFS and comparable OS to PA in early-stage HCC patients,[13,14] although some show varied results for HCC $\leq$ 2 cm.[15–18] LLR and OLR have shown similar RFS and OS in multiple studies,[19–22] while LLR showed superior RFS and comparable OS compared to PA.[23–25] However, due to variations. In study populations among cohort studies, conclusive evidence favoring one treatment over the other remains lacking.

While conducting a large-sample, multi-arm RCT would be ideal for comprehensive evaluation of these treatments,[26] sample size requirements complicate this approach.[27] Besides, current two-group RCTs lack consistency in patient populations, thereby impeding direct comparisons among OLR, LLR and PA. This study aims to address these gaps by simultaneously analyzing short-term and long-term outcomes of OLR, LLR and PA in BCLC stage 0-A HCC patients using advanced generalized propensity score analysis (GPSA) methods which are developed for concurrent multi-arm treatment comparisons, providing a higher level of evidence for clinical outcomes of these three curative therapies.

Materials and Methods

Study Design and Patients

This study was a retrospective observational cohort study and following the STROBE guidelines.[28] It was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University, and the requirement for informed consent was waived due to the nature of the retrospective cohort study. The confidentiality of patient data was ensured, and the study was performed according to the Declaration of Helsinki. From January 1, 2012 to December 31, 2021, data from consecutive patients who received curative OLR, LLR or ablation at the First Affiliated Hospital of Sun Yat-sen University were collected. All patients were followed up at the end of 2023. All patients were diagnosed according to the guidelines of the European Association for the Study of the Liver (EASL).[29]

The inclusion criteria were as follows: 1) primary HCC with pathological confirmation, 2) no previous cancer-related therapies, 3) with very-early-stage or early-stage HCC (BCLC stage 0-A), 4) receiving curative therapies and 5) Eastern Cooperative Oncology Group performance status of 0–1. The following exclusion criteria were considered: 1) with history of other malignancies, 2) with visible tumor thrombus or identified extrahepatic metastasis and 3) with insufficient clinical or follow-up information. According to the center's policies, each patient was discussed in a multidisciplinary team (MDT) meeting which included liver surgeons, radiologists and interventional oncologist.

Exposures

Open Liver Resection

OLR was performed by experienced surgeons with more than 10 years of liver surgery experience in the study center. Patients were placed in a supine position and intraoperative ultrasound was routinely performed. Pringle's maneuver was routinely used with a clamp/unclamp time of 10/5 min. An ultrasonic scalpel was used for liver parenchymal transection.

Laparoscopic Liver Resection

For LLR, the patient was placed in a supine position and the camera port was placed above the umbilicus. Carbon dioxide pneumoperitoneum pressure was maintained at 12–14 mmHg.

The choice of the type of liver resection was mainly determined by MDT according to the liver function, tumor location and tumor size.

Percutaneous Ablation

As previously described,[30] PA was performed by two experienced doctors with more than 10 years of tumor ablation experience. Ablation was performed using real-time ultrasound or computed tomography (CT) guidance. The choice of imaging-guided percutaneous ablation, including radiofrequency ablation, microwave ablation, ethanol injection and combination ablation, mainly depends on the tumor size and location.

Follow-Up

Treatment response was evaluated by contrast-enhanced CT or magnetic resonance imaging (MRI) examination 1 month after liver resection or ablation. Thereafter, all HCC patients were followed up by conventional ultrasound, contrast-enhanced ultrasound, CT or MRI, and serum alpha-fetoprotein (AFP) level every 3 months for the first 2 years, every 6 months from 2 to 5 years, and annually after 5 years. The diagnosis of recurrence was based on the guidelines of EASL.[29]

Potential Confounders

Preoperative variables, including sex, age, HBV infection, cirrhosis, Child-Pugh class, tumor number, tumor size, tumor site, AFP, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were considered as potential confounders due to these factors were essential for clinical decision and treatment strategy making.

Outcomes

The primary outcome of this study was OS. OS was defined as the time interval from surgery or ablation to death or censoring at last follow-up (31 December 2023). Another long-term outcome was RFS as a secondary outcome. RFS was defined as the time interval from surgery to recurrence or censoring at the end of follow-up. Other secondary outcomes included postoperative hospital stay and postoperative complications. Surgical complications were classified according to the Clavien-Dindo classification.[31]

Generalized Propensity Score Analysis

Since there were three treatment groups to compare concurrently in this study, to reduce the bias of potential confounders, various GPSA methods for multiple treatment comparisons were performed.[32] In GPSA, generalized propensity scores (GPS) are usually estimated using the multinomial logistic regression or generalized boosted model with multiple treatment groups as the outcome variable and potential confounding variables as covariates.[33] The GPS matching and the generalized boosted model-based inverse probability weighting are two common methods with target inference of average treatment effect for data with multiple treatment groups.[33,34] However, GPS matching would reduce more than half of the sample size after matching. Results after inverse probability weighting would be violated by extreme propensity scores.[35] Therefore, more weighting methods were recently introduced to avoid extreme propensity scores. The overlap weighting and matching weights were introduced by providing average treatment effects in the overlap population and subset, respectively.[36,37] These weights were also computed from GPS with different formulas other than inverse probability weighting. We then compared their performance on balancing confounding factors by using kernel density plots and absolute standardized mean differences (SMDs). The average SMD of each covariate <0.1 was considered to be well balanced.[38] Finally, we performed Three-way matching, TriMatch, TriMatch with exact matching, inverse probability weighting, inverse probability weighting with trimming, overlap weighting and matching weights analysis by including the potential confounders mentioned above, and selected the most appropriate method with better performance of balance for further statistical analyses.

Statistical Analysis

As the retrospective nature of the study, the sample size was determined by the study period and not conducted using statistical estimation. The baseline characteristics and outcomes were described and compared among the three study

groups in both the unmatched and matched/weighed cohorts. Continuous variables with normal distribution were described using mean and standard deviation (SD) or median and interquartile range (IQR), if data are not normally distributed. ANOVA or Kruskal–Wallis tests were used to compare the differences among the three study groups if appropriate. Categorical variables were described using frequencies and proportions and compared among three study groups using the chi-square test or Fisher's exact test. Missing covariates were imputed by its median value as a very small portion of missing were found (<1%).

Survival analysis for the three groups were estimated using the Kaplan–Meier curve, and compared by the Log rank test. Univariable and multivariable Cox proportional hazard models were performed to evaluate the treatment effect of the three study groups with OS and RFS both before and after GPSA. The multivariable Cox model included all the potential confounders mentioned above. Hazard ratio (HR) and its 95% confidence interval (95% CI) was estimated for each Cox model. Proportional hazard assumption was tested by weighted residuals using *cox.zph* function in R and no violation was found. Subgroup analysis was performed according to BCLC stage (0 and A). The P value was corrected by Bonferroni method for multiple treatment comparisons. Flexible parametric survival regression standardization was used to estimate standardized survival.[39,40] The hazard which was defined as the slope of the survival curve and the hazard difference between OS and RFS of intergroups before and after GPSA were reported by graphs over time.

One of the authors QZ a medical statistician performed the statistical analysis. A two-tailed p value less than 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.6.0 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

A total of 1778 patients with BCLC stage 0-A HCC met the study inclusion criteria, 1237 of which were treated with OLR, 307 underwent LLR and 234 underwent PA (Figure 1). The baseline characteristics of the 1778 patients were summarized in Table 1. Most characteristics of the three groups were unbalanced before adjustment. Of note, compared with the LLR and PA groups, the tumor size in the OLR group was significantly larger, and the proportion of tumors in the bilobar liver was significantly higher. While compared with the OLR and LLR groups, the proportion of multifocal tumors was significantly higher in the PA group. Therefore, seven GPSA methods were conducted to balance the covariates among the OLR, LLR and PA groups. SMD (Figures 2A and S1) and density plot of GPS (Figure 2B) were used to assess the effects of balancing. As represented by the overlap weighting, all the SMDs with baseline characteristics were <0.1 (Table 1 and Figure 2A) and the overlap of density plots of GPS for each group (Figure 2B) was reasonable, suggesting that the potential confounders were well balanced with no significant differences in preoperative variables among the three groups.

Intraoperative and Postoperative Outcomes

As Table S1 shown, the operation time was significantly longer in the LLR group compared with the OLR group (4.25 hours vs 3.20 hours, $P < 0.001$). In addition, more intraoperative blood loss was observed in the OLR group compared with the LLR group ($P = 0.001$). Conversion to open surgery occurred in 32 patients in the LLR group due to: uncontrollable bleeding (n = 7), difficulty in dissecting tumor from major vessels (n = 11), and poor exposure or no progression after a long time (n = 14). In the PA group, most of the patients (n = 182) underwent radiofrequency ablation, 17.1% (n = 40) underwent microwave ablation, 4.3% (n = 10) underwent ethanol injection, and the remaining underwent combination ablation. There was no intraoperative death in the three groups.

After overlap weighting in Table 2, patients in the LLR and PA groups recovered significantly faster than those in the OLR group (7 days vs 3 days vs 9 days, $P < 0.001$). The incidence of postoperative complications was significantly higher in the LLR group compared with the OLR and PA groups ($P < 0.001$). However, the postoperative complications were more severe in the OLR group compared with LLR and PA groups (Clavien-Dindo grade II: $P = 0.022$; Clavien-Dindo grade IIIa: $P = 0.007$) while most of postoperative complications in LLR and PA groups were Clavien-Dindo grade I. Notably, five patients occurred liver failure and one patient occurred multiple organ dysfunctional syndromes in

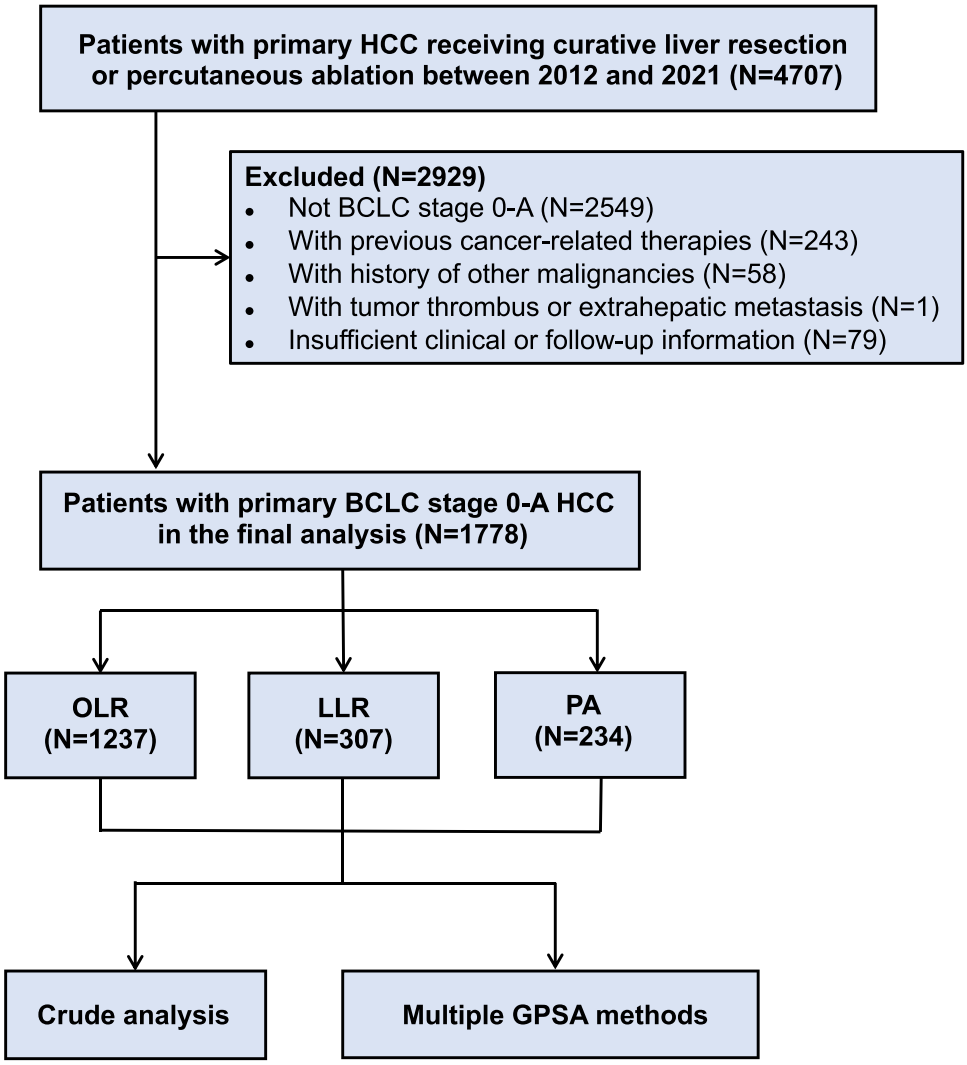

Figure 1 Flow diagram of patient collection. A total of 1778 patients with BCLC stage 0-A HCC which met the study inclusion criteria (OLR: 1237; LLR: 307; PA: 234) were included for analysis.
Abbreviations: HCC, hepatocellular carcinoma; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation; GPSA, generalized propensity score analysis.

the OLR group, and one patient occurred liver failure in the LLR group. No early postoperative death occurred in any of the three groups, suggesting the safety of these three treatments.

Long-Term Oncological Outcomes

The median follow-up time for all patients was 39.5 (22.2, 63.5) months. Before GPSA, the 5-year OS rates of OLR, LLR and PA groups were 71.3%, 84.0% and 81.3%, respectively ($P < 0.001$, Figure 3A). After the overlap weighting, the 5-year OS rates of the OLR, LLR and PA groups were 79.7% versus 89.1% versus 84.0%, respectively ($P = 0.020$, Figure 3B). Compared with patients in the LLR and PA groups, patients in the OLR group had a significantly shorter OS. Before GPSA, the 5-year RFS rates of OLR, LLR and PA groups were 41.2%, 49.5% and 34.8%, respectively ($P < 0.001$, Figure 3C). After the overlap weighting, the 5-year RFS rates of OLR, LLR and PA groups were 48.0% versus 55.6% versus 30.3%, respectively ($P < 0.001$, Figure 3D). Patients in the LLR group had a significantly longer RFS than those in the OLR and PA groups. As shown in Figure S2, consistent with the results obtained by overlap weighting analysis, the results obtained by other GPSA methods except Three-way matching analysis also showed superior long-term outcomes in the LLR group.

Table 1 Baseline Characteristics of HCC Patients Included Before and After Generalized Propensity Score Analysis

Variable	Entire Crude Analysis					Overlap Weighting Analysis				
	OLR (n=1237)	LLR (n=307)	PA (n=234)	*P* value	SMD	OLR (n=1237)	LLR (n=307)	PA (n=234)	*P* value	SMD
Age (year)	54.28 (45.28, 62.07)	54.04 (46.97, 61.16)	56.92 (48.75, 65.93)	0.001	0.214	56.29 (48.58, 63.83)	55.49 (49.33, 62.95)	55.22 (47.41, 64.34)	0.963	0.011
Sex				0.157	0.086				0.725	0.050
Male	1073 (86.7)	266 (86.6)	192 (82.1)			1053.2 (85.1)	260.4 (84.8)	204.5 (87.4)		
Female	164 (13.3)	41 (13.4)	42 (17.9)			183.8 (14.9)	46.6 (15.2)	29.5 (12.6)		
HBV infection				0.437	0.071				0.596	0.052
No	200 (16.2)	42 (13.7)	41 (17.5)			198.2 (16.0)	40.7 (13.3)	34.8 (14.9)		
Yes	1037 (83.8)	265 (86.3)	193 (82.5)			1038.8 (84.0)	266.3 (86.7)	199.2 (85.1)		
Cirrhosis				0.067	0.111				0.717	0.044
No	539 (43.6)	133 (43.3)	83 (35.5)			484.3 (39.1)	110.5 (36.0)	89.8 (38.4)		
Yes	698 (56.4)	174 (56.7)	151 (64.5)			752.7 (60.9)	196.5 (64.0)	144.2 (61.6)		
ALT (IU/L)	32.50 (23.00, 49.00)	29.00 (20.00, 41.50)	29.00 (22.00, 44.75)	0.001	0.108	30.00 (21.00, 42.00)	29.00 (20.00, 40.92)	28.00 (20.00, 42.77)	0.454	0.058
AST (IU/L)	34.00 (26.00, 49.00)	30.00 (24.00, 40.50)	33.00 (24.00, 44.00)	<0.001	0.202	31.00 (24.00, 39.00)	30.00 (23.00, 41.00)	31.00 (22.19, 40.00)	0.922	0.044
AFP (ng/mL)				0.030	0.094				0.790	0.034
≤20	522 (42.2)	151 (49.2)	114 (48.7)			621.2 (50.2)	146.3 (47.7)	113.9 (48.7)		
>20	715 (57.8)	156 (50.8)	120 (51.3)			615.8 (49.8)	160.7 (52.3)	120.1 (51.3)		
Child-Pugh class				0.031	0.152				0.268	0.091
A	1165 (94.2)	297 (96.7)	214 (91.5)			1186.7 (95.9)	289.4 (94.3)	217.2 (92.8)		
B	72 (5.8)	10 (3.3)	20 (8.5)			50.3 (4.1)	17.6 (5.7)	16.8 (7.2)		
Tumor number				<0.001	0.299				0.999	0.010
1	1206 (97.5)	289 (94.1)	203 (86.8)			1129.7 (91.3)	280.8 (91.5)	214.2 (91.5)		
2	22 (1.8)	17 (5.5)	24 (10.3)			95.9 (7.8)	23.1 (7.5)	17.5 (7.5)		
3	9 (0.7)	1 (0.3)	7 (3.0)			11.4 (0.9)	3.1 (1.0)	2.3 (1.0)		
Tumor size (cm)				<0.001	1.040				0.988	0.030
≤2	65 (5.3)	43 (14.0)	103 (44.0)			291.8 (23.6)	74.2 (24.2)	53.4 (22.8)		
>2, ≤5	541 (43.7)	187 (60.9)	127 (54.3)			889.6 (71.9)	220.3 (71.8)	169.4 (72.4)		
>5	631 (51.0)	77 (25.1)	4 (1.7)			55.7 (4.5)	12.5 (4.1)	11.2 (4.8)		
Tumor site				<0.001	0.393				0.820	0.063
Left	242 (19.6)	109 (35.5)	28 (12.0)			250.5 (20.2)	58.2 (19.0)	48.0 (20.5)		
Right	881 (71.2)	180 (58.6)	189 (80.8)			916.1 (74.1)	224.6 (73.2)	172.8 (73.8)		
Bilobar	114 (9.2)	18 (5.9)	17 (7.3)			70.4 (5.7)	24.2 (7.9)	13.2 (5.6)		

Abbreviations: HCC, hepatocellular carcinoma; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation; SMD, standardized mean difference; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein.

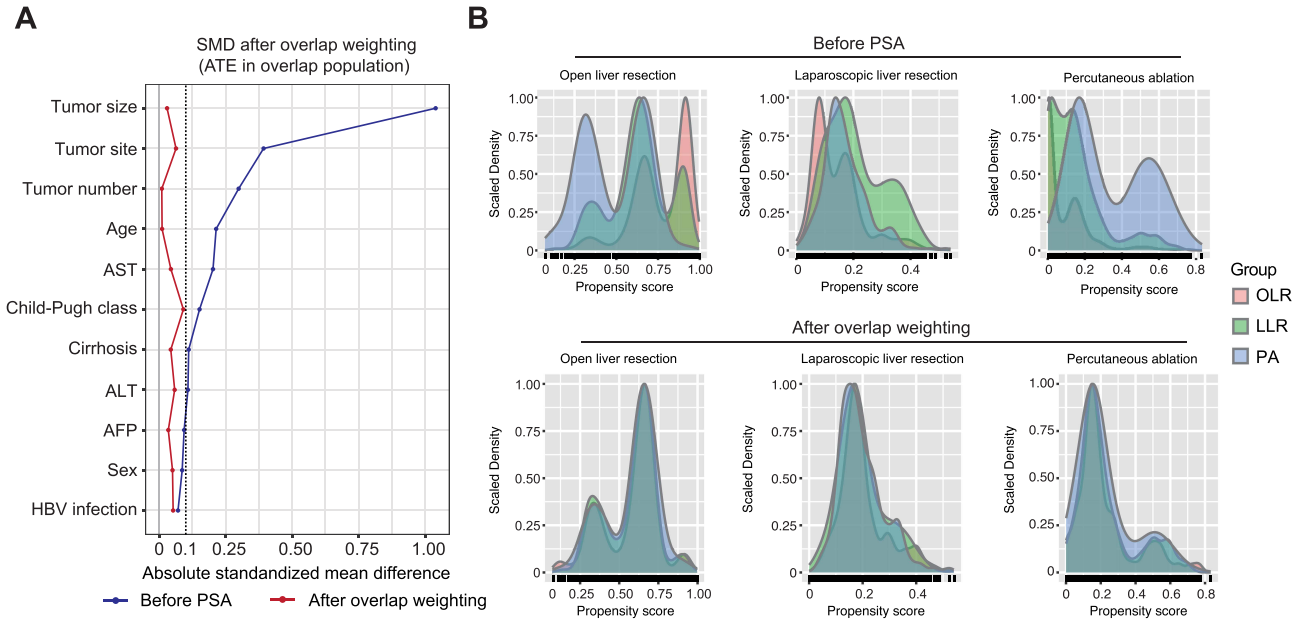

Figure 2 Assessment of balance of overlap weighting analysis. (**A**) The absolute SMDs of potential confounders before and after overlap weighting analysis. (**B**) Density plot of generalized propensity score in OLR, LLR and PA groups before and after overlap weighting analysis.
Abbreviations: ATE, average treatment effect; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; SMD, standardized mean difference; PSA, propensity score analysis; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation.

Univariable and multivariable Cox proportional hazard analyses were performed before and after GPSA to evaluate the relationships between the three treatment options and OS or RFS (Table 3). LLR was independently associated with better RFS compared with OLR (LLR vs OLR: HR=0.74, P = 0.006) and PA (PA vs LLR: HR = 1.69, P < 0.001) in crude multivariable Cox analysis and was also significantly better than OLR (LLR vs OLR: HR = 0.70, P = 0.016) and PA (PA vs LLR: HR = 1.83, P < 0.001) in overlap-weighted multivariable Cox analysis. In terms of OS, LLR was independently associated with better OS compared with OLR in crude (LLR vs OLR: HR = 0.61, P = 0.014) and overlap-weighted multivariable Cox analysis (LLR vs OLR: HR = 0.49, P = 0.015). No significant difference was observed between LLR and PA groups or PA and OLR groups in crude or overlap-weighted multivariable Cox analysis (both P > 0.05), suggesting LLR or OLR was not independently associated with better OS compared to PA.

The hazards of all-cause mortality and recurrence over time among the three groups after overlap weighting were shown in Figure 4. The hazard of all-cause mortality reached the highest level within a year and remained unchanged thereafter (Figure 4A). LLR showed the lowest hazard of all-cause mortality and followed by PA, but there was no significant difference between the two groups. However, the hazards of mortality in both LLR and PA were significantly lower than that of OLR. The hazard differences with 95% CI were depicted in Figure S3A. The hazard of recurrence rose to the highest level within half a year, then fell back in 1 year, and decreased slightly over time after 1 year, suggesting the highest risk of tumor recurrence a half-year after OLR, LLR or PA (Figure 4B). PA showed the lowest hazard of recurrence compared to LLR, and LLR showed the lower hazard of recurrence compared with OLR. The hazard differences of recurrence with 95% CI were depicted in Figure S3B.

Subgroup Analysis

Subgroup analysis was performed according to the BCLC stage (0 and A) in both the original and overlap weighted cohort. The results obtained by overlap weighting analysis were depicted as below. In the BCLC stage 0 HCC patients, although no statistically significant differences in the OS and RFS were observed among the three groups, the Kaplan–Meier curves and multivariable Cox proportional hazard analyses showed that patients in the LLR group tended to have better RFS compared with the OLR and PA groups (Table S2, Figure S4A and B). In the BCLC stage A cohort, consistent with the whole population, patients in the LLR group had significantly longer RFS than those in the OLR and PA groups, and patients in the LLR and PA groups tended to have better OS compared with the OLR group (Table S3, Figure S4C and D).

Table 2 Postoperative Data of HCC Patients Before and After Generalized Propensity Score Analysis

Variable	Entire Crude Analysis				Overlap Weighting Analysis			
	OLR (n=1237)	LLR (n=307)	PA (n=234)	*P* value	OLR (n=1237)	LLR (n=307)	PA (n=234)	*P* value
Postoperative complication (%)				<0.001				<0.001
Yes	321 (25.9)	88 (28.7)	16 (6.8)		298.0 (24.1)	91.2 (29.7)	16.3 (7.0)	
No	916 (74.1)	219 (71.3)	218 (93.2)		939.0 (75.9)	215.8 (70.3)	217.7 (93.0)	
General complication (%)								
Pulmonary infection	23 (1.9)	3 (1.0)	0 (0.0)	0.070	28.7 (2.3)	3.5 (1.1)	0.0 (0.0)	0.146
Surgical complication (%)								
Abdominal bleeding	12 (1.0)	0 (0.0)	0 (0.0)	0.071	10.4 (0.8)	0.0 (0.0)	0.0 (0.0)	0.205
Gastrointestinal bleeding	2 (0.2)	0 (0.0)	0 (0.0)	0.645	2.7 (0.2)	0.0 (0.0)	0.0 (0.0)	0.659
Liver-related complication (%)								
Bile leakage	12 (1.0)	0 (0.0)	0 (0.0)	0.071	7.0 (0.6)	0.0 (0.0)	0.0 (0.0)	0.347
Mixed complication (%)								
Subphrenic abscess	1 (0.1)	0 (0.0)	0 (0.0)	0.803	0.1 (0.0)	0.0 (0.0)	0.0 (0.0)	0.887
Abdominal infection	12 (1.0)	0 (0.0)	0 (0.0)	0.071	8.8 (0.7)	0.0 (0.0)	0.0 (0.0)	0.271
Intestinal obstruction	4 (0.3)	1 (0.3)	0 (0.0)	0.684	3.7 (0.3)	0.1 (0.0)	0.1 (0.0)	0.388
Major complication (%)								
Postoperative liver failure	5 (0.4)	1 (0.3)	0 (0.0)	0.620	5.1 (0.4)	0.3 (0.1)	0.0 (0.0)	0.382
MODS	1 (0.1)	0 (0.0)	0 (0.0)	0.803	1.4 (0.1)	0.0 (0.0)	0.0 (0.0)	0.806
Clavien-Dindo grade (%)								
I	180 (14.6)	62 (20.2)	16 (6.8)	<0.001	185.8 (15.0)	61.0 (19.9)	16.3 (7.0)	0.003
II	68 (5.5)	9 (2.9)	0 (0.0)	<0.001	53.5 (4.3)	7.6 (2.5)	0.0 (0.0)	0.022
IIIa	62 (5.0)	16 (5.2)	0 (0.0)	0.002	46.7 (3.8)	22.4 (7.3)	0.0 (0.0)	0.007
IIIb	5 (0.4)	0 (0.0)	0 (0.0)	0.334	5.6 (0.5)	0.0 (0.0)	0.0 (0.0)	0.458
IVa	5 (0.4)	1 (0.3)	0 (0.0)	0.62	5.1 (0.4)	0.3 (0.1)	0.0 (0.0)	0.382
IVb	1 (0.1)	0 (0.0)	0 (0.0)	0.803	1.4 (0.1)	0.0 (0.0)	0.0 (0.0)	0.806
Postoperative stay (days)	9.00 (8.00, 11.00)	7.00 (5.00, 9.00)	3.00 (2.00, 4.00)	<0.001	9.00 (8.00, 11.00)	7.00 (5.00, 8.00)	3.00 (2.00, 4.00)	<0.001

Abbreviations: HCC, hepatocellular carcinoma; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation.

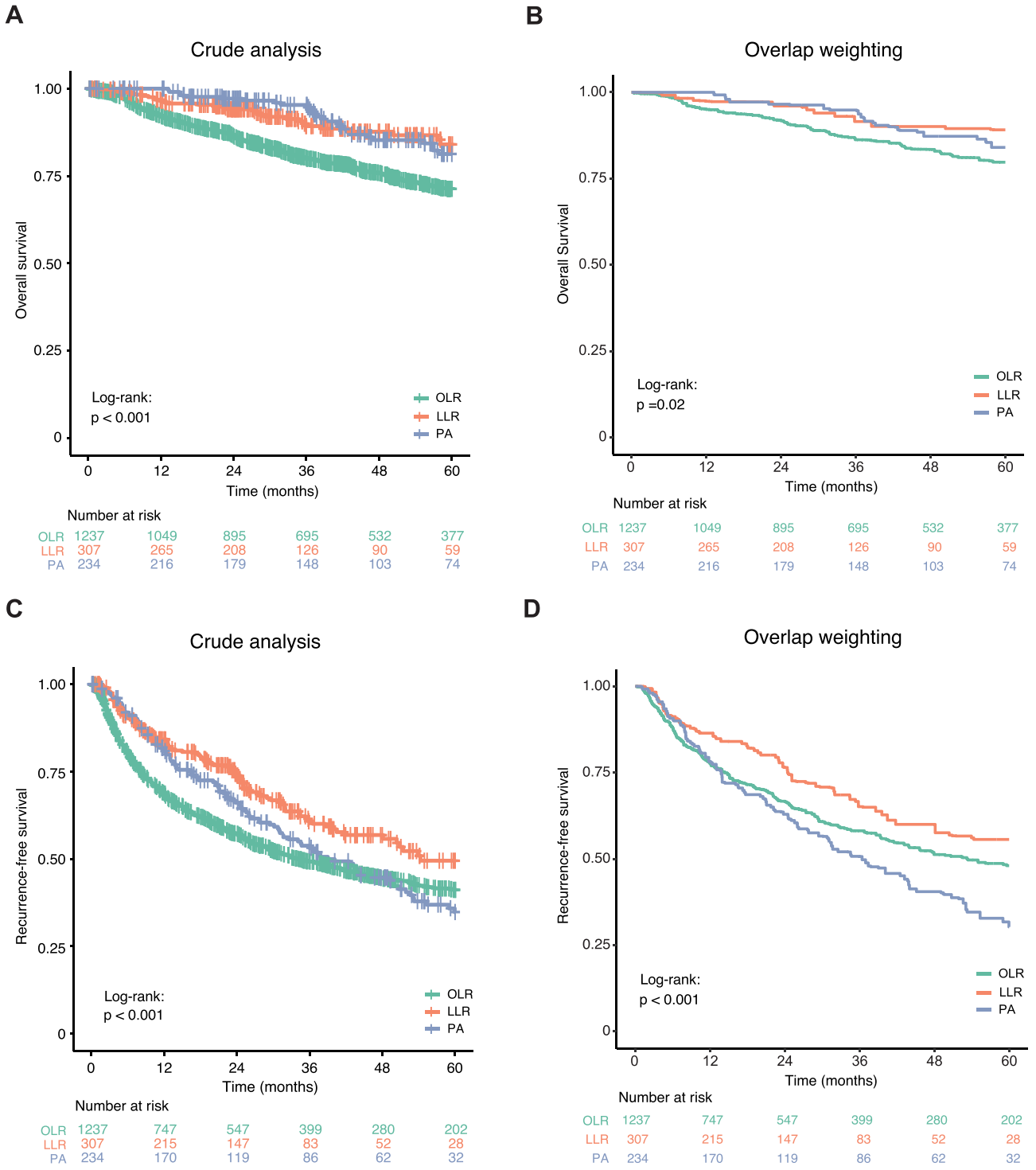

Figure 3 Kaplan–Meier curves for long-term outcomes of BCLC stage 0-A HCC patients who underwent OLR, LLR and PA before and after overlap weighting analysis. (**A** and **B**) Overall survival before (**A**) and after (**B**) overlap weighting analysis. (**C** and **D**) Recurrence-free survival before (**C**) and after (**D**) overlap weighting analysis.
Abbreviations: HCC, hepatocellular carcinoma; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation.

Discussion

Minimally invasive techniques, including laparoscopic hepatectomy and percutaneous ablation, have been well developed in the treatment of HCC. According to the Balliol IDEAL classification, long-term oncological outcomes are recommended to evaluate the efficacy of laparoscopic hepatectomy in treating HCC.[41] However, high-level studies on

Table 3 Univariable and Multivariable Cox Proportional Hazards Modeling for RFS and OS in HCC Patients Before and After Generalized Propensity Score Analysis

	Crude Analysis				Overlap Weighting Analysis			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
RFS								
LLR vs OLR	0.64 (0.52, 0.79)	<0.001	0.74 (0.60, 0.92)	0.006	0.74 (0.56, 0.98)	0.035	0.70 (0.53, 0.94)	0.016
PA vs OLR	0.90 (0.74, 1.10)	0.309	1.25 (0.99, 1.58)	0.059	1.32 (1.05, 1.66)	0.019	1.29 (1.01, 1.64)	0.040
PA vs LLR	1.40 (1.08, 1.83)	0.012	1.69 (1.28, 2.25)	<0.001	1.79 (1.31, 2.43)	<0.001	1.83 (1.33, 2.51)	<0.001
OS								
LLR vs OLR	0.47 (0.32, 0.69)	<0.001	0.61 (0.41, 0.91)	0.014	0.52 (0.30, 0.92)	0.025	0.49 (0.28, 0.87)	0.015
PA vs OLR	0.49 (0.33, 0.73)	<0.001	0.74 (0.48, 1.16)	0.195	0.66 (0.41, 1.07)	0.092	0.67 (0.41, 1.09)	0.109
PA vs LLR	1.03 (0.61, 1.74)	0.910	1.22 (0.71, 2.11)	0.478	1.27 (0.64, 2.49)	0.495	1.37 (0.69, 2.71)	0.366

Abbreviations: HCC, hepatocellular carcinoma; OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation; RFS, recurrence-free survival; OS, overall survival.

long-term outcomes in BCLC stage 0-A HCC patients after OLR, LLR or PA are lacking. Due to the challenges of conducting multi-arm randomized controlled trials in clinical practice, we employed multiple GPSA methods to balance baseline characteristics of the study cohorts, aiming for more reliable comparisons in real-world settings. Our study found that patients in the minimally invasive group (LLR and PA groups) had significantly fewer postoperative complications and faster recovery compared with patients who underwent OLR. Moreover, patients in the LLR group had significantly longer RFS compared with patients in the OLR and PA groups and significantly longer OS compared with patients in the OLR group. These findings demonstrated LLR as an effective and safe approach in the treatment of BCLC stage 0-A HCC.

The debate over whether resection or ablation is the superior treatment for BCLC stage 0-A HCC has been extensively discussed previously. Accumulating evidence, including high-level systematic reviews and meta-analysis, consistently indicates that liver resection yields better RFS than ablation while provides similar OS for HCC patients.[13,14,42,43] In line with these findings, our study also revealed that patients in the either LLR or OLR group had significant longer RFS than

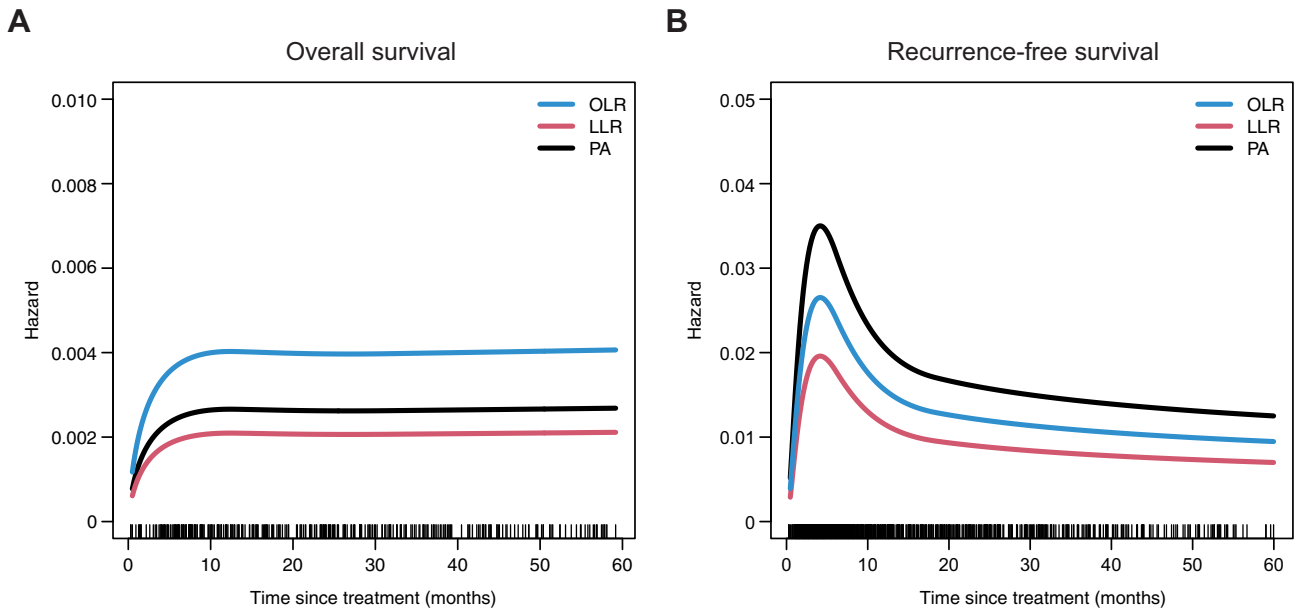

Figure 4 The hazards of all-cause mortality and recurrence over time among three groups after overlap weighting. (**A**) Overall survival, (**B**) Recurrence-free survival.
Abbreviations: OLR, open liver resection; LLR, laparoscopic liver resection; PA, percutaneous ablation.

those in the PA group. However, upon further stratification of patients receiving liver resection into OLR and LLR groups, we found that patients in the PA group had similar OS to those in the LLR group and longer OS than those in the OLR group. The superior RFS associated with surgical resection is likely attributed to the complete removal of tumors, thereby eliminating micro metastases. Conversely, the high recurrence rates observed after ablation might be attributed to repeated puncture to the tumor, the change of biological behaviors of tumor cells and the remodeling of tumor microenvironment.[44] Despite the shorter RFS, percutaneous ablation could provide comparable OS mainly due to the repeatability of ablation for tumor recurrence.[45] In terms of short-term outcomes, patients undergoing ablation showed less postoperative complication rate and faster recovery compared with the surgical group (LLR and OLR groups), suggesting that PA is a more minimally invasive approach and might be associated with better quality of life.

Moreover, in our study, the LLR group showed significantly better OS and RFS than OLR group in patients receiving a hepatectomy. A recent prospective observational study using propensity score matching with 56 patients for each group compared long-term outcomes of laparoscopic and open liver resection for patients with BCLC stage 0-A HCC, and found that there was no significant difference between the laparoscopic and open hepatectomy groups in the 5-year RFS and OS.[19] Similarly, other studies also showed that LLR and OLR provided comparable RFS and OS.[20–22] However, of note, Zhu P et al[19] study found that when they combined LLR and robotic-assisted liver resection into a group (minimally invasive hepatectomy group), the 5-year RFS rate was lower in the minimally invasive hepatectomy group compared to OLR, consistent with our findings. The lower RFS rates observed after minimally invasive hepatectomy may be attributed to the potential reduced immunosuppressive effects associated with minimally invasive treatments.[46,47] Additionally, the type of hepatectomy might account for these differences in our study. In our study, the proportions of patients receiving anatomical hepatectomy was significantly higher in the LLR group than in the OLR group, also suggesting the safety of the laparoscopic hepatectomy. It is suggested that LLR may facilitate the complete removal of tumor burden and potential micro metastases, such as microvascular invasion, which could explain its superior RFS and OS outcomes. In addition, the LLR group showed lower complication rates and shorter postoperative stays than the OLR group, yielding better short-term outcomes. Given short-term and long-term outcomes, LLR might be a superior treatment option for BCLC stage 0-A HCC if the preserve of liver function is allowed. Overall, our results demonstrate the safety and efficacy of LLR for patients with BCLC stage 0-A HCC.

Due to the minimally invasiveness and therapeutic efficacy of laparoscopic hepatectomy for HCC patients, the adoption of laparoscopic hepatectomy has increased rapidly in the recent years. The indications for LLR are uncertain, and several factors, including tumor size, location, type/extent of liver resection and presence of liver cirrhosis, affect the complexity of LLR.[48] Therefore, it is cautious for surgeons to select patients available for LLR. Currently, according to the EASL guideline, LLR is appropriate for very early and early HCC mainly located in superficial or antero-lateral liver positions.[29] Nevertheless, the role of LLR in some situations remains controversial, such as for difficultly located HCC and for multiple or giant lesions. Owing to the rapidly developed techniques, laparoscopic hepatectomy for liver segments, which were difficult to resect, such as S1, S7 and S8, have been conducted at some specialized centers, suggesting that more and more HCC patients could benefit from LLR.[49] As a minimally invasive approach, LLR provides better RFS and OS compared to OLR, while another minimally invasive approach, percutaneous ablation, is restricted by tumor location and inappropriate for lesions located near large vessels, such as a primary or secondary branch of the portal vein, subphrenic lesions and lesions near extrahepatic organs.[50] In recent years, a growing number of evidence has found that laparoscopic ablation could overcome the technique difficulty of percutaneous ablation and provided better therapeutic outcomes than percutaneous ablation for subphrenic lesions, suggesting the superiority of the laparoscopic approach.[51,52] Therefore, despite the complexity and difficulty of LLR, it is worthy of promoting to surgeons.

There were a few limitations in this study. First, this study was still a non-randomized study which might lead to some unavoidable bias. Thus, we performed various GPSA methods to overcome potential bias and several methods achieved excellent balance. And most of the results from those methods were consistent. Second, this study was conducted at a single institution, and whether our findings could be generalized to other centers was unknown. Third, most patients included in this study had hepatitis B. It is unknown whether our conclusions could be obtained in HCC patients with other etiological factors. In the future, multicenter randomized controlled trials with large sample sizes are required for further validation.

Conclusion

In conclusion, laparoscopic hepatectomy was safe and effective for the treatment of patients with BCLC stage 0-A HCC in this large observational cohort study after using various covariates adjustment analysis methods suitable for concurrent multiple treatment comparisons. Laparoscopic hepatectomy is not only minimally invasive but also provides superior long-term outcomes compared with open liver resection and percutaneous ablation.

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Disclosure

The authors report no conflicts of interest in this work.

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