Updates in Surgery (2025) 77:1451–1462
https://doi.org/10.1007/s13304-025-02293-z

ORIGINAL ARTICLE

Robotic vs laparoscopic resection for hepatocellular carcinoma: multicentric propensity-score matched analysis of surgical and oncologic outcomes in 647 patients

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Received: 13 December 2024 / Accepted: 6 June 2025 / Published online: 20 July 2025

Abstract

Background and Objectives Laparoscopic liver resection (LLR) for hepatocellular carcinoma (HCC) has been linked to several advantages compared to open approach, but the actual benefit of robotic liver resection (RLR) over LLR in HCC needs further investigation.

Methods We performed a multicentric propensity-score matched (PSM) analysis comparing perioperative and oncologic outcomes of LLR vs. RLR for HCC. The PSM model was estimated using a multivariable logistic regression, with type of surgery as dependent variable and age, BMI, clinically-significant portal hypertension, αFP, size of principal lesion, number of nodules and Kawaguchi difficulty score as covariates. Overall (OS) and recurrence-free (RFS) survivals were estimated using the Kaplan–Meier method.

Results Six-hundred-forty-seven HCC patients from 12 IGoMILS registry centers treated by LLR (553 patients) or RLR (94 patients) were included. After PSM, RLR resulted in wider surgical margins (median: 10 vs 5 mm; $p=0.002$) with higher prevalence of R0 resection (98.9 vs 93.1%; $p=0.037$), lower conversion rate (2.1 vs. 8.5%; $p=0.039$) and shorter hospital stay (median: 4 vs 5 days; $p=0.025$), with no significant difference in postoperative complication rate. We observed similar OS among RLR and LLR cohorts [5-y OS: 68.7 vs 65.0%; univariable HR = 0.95 (95% CI: 0.60–1.49); $p=0.82$], with significantly better RFS in RLR cohort [5-y RFS: 46.8 vs 24.0%; univariable HR = 0.71 (95% CI: 0.52–0.98); $p=0.04$].

Conclusions Perioperative outcomes were significantly better in the RLR cohort, with a lower conversion rate and shorter hospital stay, although the latter may be influenced by the multi-institutional study design. Notably, we observed wider resection margins in the RLR group, which were associated with significantly improved RFS.

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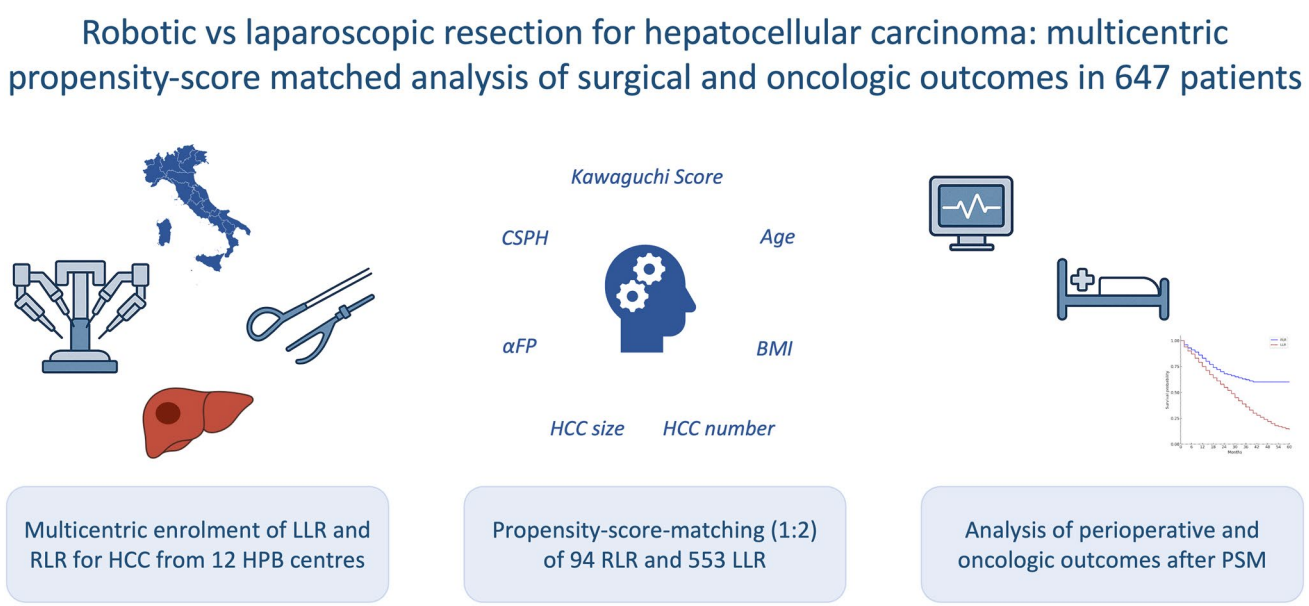
Graphical Abstract



Keywords Hepatocellular Carcinoma · Robotic Liver Resection · Laparoscopic Liver Resection · Minimally Invasive Liver Surgery · Oncologic Outcomes

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide [1]. Surgical approaches such as liver transplantation (LT) and liver resection (LR) represent the most effective treatments for HCC [2] in terms of tumor-related outcomes. LT has been acknowledged as the best curative option, but is limited by several factors such as i) medical/social contraindications, ii) tumor burden, iii) drop-out risk for tumor progression, iv) donor shortage [3]. On the other hand, LR represents a schedulable and accessible treatment, and is, therefore, regarded as the first-line treatment option for HCC according to several algorithms [4, 5].

Development and implementation of laparoscopic liver resection (LLR) over the last decades resulted in improved perioperative outcomes with shorter hospital stay [6, 7], and easier surgical management of recurrences [8–10]. More importantly, LLR allowed a safe expansion of surgical indication to those patients presenting clinically significant portal hypertension (CSPH)[11, 12]: as a consequence, LLR should be considered as the gold standard approach for surgical resection in the HCC setting.

The advent of the DaVinci robotic platform represented a breakthrough for several fields of surgery[13–18]: tremor mitigation, magnified 3-dimensional and stable vision, instrument flexibility and increased dexterity in narrow spaces were just some of the robot advantages that may facilitate surgical dissection and liver manipulation.

Benefits of RLR for HCC have already been investigated in a recently published series, highlighting significantly better perioperative outcomes with similar oncologic results compared to the traditional open approach [19]. Such benefits are less evident when comparing RLR and LLR, as pointed out by contrasting results from several systematic reviews and metanalyses [20, 21]. In particular, the comparison of RLR and LLR in the HCC setting has been poorly investigated so far [22–26].

Given this background, we sought to compare perioperative and oncologic outcomes of RLR and LLR in a multicentric, PSM population of HCC patients included in the IGoMILS registry.

Methods

Data were extracted from the Italian Group for Minimally Invasive Liver Surgery (IGoMILS) registry, a prospective national registry covering all minimally-invasive liver resections performed in 79 national collaborative centers since November 2014 [27]

Study design and aims

We performed a retrospective multicentric cohort study including all cases of liver resection for HCC registered from November 2014 to June 2019 in 12 adhering centers.

Patient and tumor characteristics, intraoperative data, surgical technique, perioperative and long-term oncologic outcomes were anonymously extracted from IGoMILS registry and analyzed.

The two treatment cohorts (LLR and RLR) were balanced through propensity score matching (PSM).

As a primary study aim, we focused on the comparison of baseline characteristics of the RLR and LLR cohort, investigating the perioperative outcomes of the two different techniques.

As a secondary study aim, we further analyzed long-term oncologic outcomes, focusing on recurrence-free and overall survivals of the two treatment cohorts.

Study variables

Baseline patient characteristics included age [years], gender, body mass index [BMI – Kg/m^2], previous abdominal surgery, Child-Turcotte-Pugh score and clinically significant portal hypertension (CSPH), defined by one of the following parameters: i) platelet count < 100,000/ul, ii) esophageal varices, iii) hypersplenism (spleen diameter > 12 cm) or iv) hepatic-venous-portal-pressure gradient > 10 mmHg.

Preoperative morpho-dimensional and biological tumor parameters such as number and size [mm] of HCC nodules and alpha-fetoprotein (αFP) values [ng/ml] were also collected.

Intraoperative data included surgical technique, application of hilar clamping, surgery duration [min], intraoperative blood loss [ml], intraoperative transfusions [units of packed red blood cells – uPRBC], intraoperative mortality and conversion to open approach.

Predicted surgical difficulty was estimated following the Kawaguchi difficulty score [28].

Postoperative pathological features such as microvascular invasion (MVI) and resection margin status were recorded.

Length of hospital stay [days], postoperative complications according to Clavien–Dindo classification [29], in-hospital mortality as well as surgical revision and re-admission were considered as perioperative outcomes.

Last, tumor recurrence and patient death dates were recorded during follow-up.

Perioperative management and surgical technique

All patients were evaluated during multidisciplinary team (MDT) meetings involving surgeons, hepatologists, diagnostic and interventional radiologists.

HCC diagnosis followed non-invasive EASL criteria [30]; impaired hepatic functional reserve (Child-Turcotte-Pugh score C, intractable ascites, platelet count < 50.000/μL) and high operative risk (American Association of Anesthesiologists score > 3) were generally considered as contraindications to resection.

All patients underwent intraoperative ultrasound for tumor and vascular mapping [31]. Intermittent pedicle clamping was selectively used according to surgeons' preferences.

LLR technique

Parenchymal transection was usually performed using cavitron ultrasonic surgical aspirator dissector [the CUSA® Excel + Cavitron Ultrasonic Surgical Aspirator System (Integra, Ireland) OR Misonix (Sonastar, USA)] and the Ultracision Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA), while hemostasis and biliostasis on the liver cut surface were achieved using metallic clips, Hem-o-lock or non-absorbable sutures.

Indocyanine green fluorescence was not routinely used during transection, and its application was left to the surgeon's discretion.

RLR technique

Robotic procedures were performed using the da Vinci Si or Xi platform (Intuitive Surgical). Parenchymal transection was performed using a Kelly clamp crush technique combined with either ultrasonic (Harmonic ACE; Intuitive Surgical) or radiofrequency (Vessel Sealer; Intuitive Surgical) energy devices.

Indocyanine green fluorescence was selectively used for intraoperative navigation during parenchymal transection, according to surgeon preference.

All patients underwent life-long surveillance according to EASL [30] guidelines.

Tumor recurrences were managed after MDT discussion.

Statistical analysis

Continuous data were reported as medians and interquartile ranges (IQR). Categorical data were reported as counts and percentages. Patients' demographic, clinical and treatment characteristics of the study population, stratified by surgical technique ("LLR" vs. "RLR") were reported.

Comparisons between LLR and RLR groups were performed using the Wilcoxon signed-rank test for continuous variables and Chi-square test or Fisher's exact test for categorical variables.

Balance in covariates between treatment groups was also evaluated by standardized mean difference (SMD). An SMD less or equal to 0.1 was deemed to be the ideal balance.

To adjust for the nonrandom assignment of the procedure, a 1:2 propensity-score matching (PSM) algorithm without replacement was used, with a caliper of 0.15.

The propensity score (PS) was estimated using multivariable logistic regression, with the type of surgery as the dependent variable and age, BMI, CSPH, αFP, size of the principal lesion, number of nodules and Kawaguchi difficulty score as covariates.

The overall survival (OS) was defined as the time from surgical treatment until death or last contact. The recurrence-free survival (RFS) was defined as the time from the date of surgery until recurrence, death or last contact. Patients who died without recurrence during postoperative follow-up were considered as having reached the RFS endpoint, rather than being censored.

OS and RFS functions were estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between surgery techniques in the pre-PSM cohort.

To evaluate the effect of surgery on OS and on RFS in the post-PSM cohort, hazard ratios (HRs) estimated from Cox proportional models, along with their 95% confidence intervals (CIs), were reported. To account for covariate imbalances, HRs were adjusted for covariates with an SMD greater than 0.1 in the post-PSM cohort [32].

All reported p-values were two sided, with p-value less than 0.05 considered as statistically significant.

All analyses were performed with the statistical software SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Patient characteristics before and after PSM are recorded in Table 1.

Starting population included 553 LLR and 94 RLR.

Patients undergoing LLR were generally older (median: 70 vs 65 years; $p < 0.001$), presenting lower BMI (median: 26 vs. 26 kg/m^2; $p = 0.013$), lower prevalence of CSPH (28.2 vs 50.0%; $p < 0.001$) and significantly higher αFP values (median: 9.7 vs 4.8 ng/ml; $p < 0.001$) compared to RLR population.

Size (median: 30 vs 30 mm; $p = 0.25$) of HCC nodules was similar among LLR and RLR groups, while the LLR population presented a higher prevalence of multinodular tumors (26.4 vs 5.3%; $p < 0.001$); conversely the Kawaguchi difficulty score distribution ($p = 0.20$), the rate of major vs. minor hepatectomy ($p = 0.76$) and the frequency of anatomical vs. non-anatomical resections ($p = 0.37$) were not significantly different among the two groups.

As described in the Methods section, PSM was performed according to age, BMI, CSPH, αFP, size of principal lesion, number of tumor nodules and Kawaguchi difficulty score, to control for the nonrandom assignment of patients to LLR or RLR.

After PSM, we identified two balanced cohorts of 188 LLR and 94 RLR.

A higher prevalence of previous abdominal surgery in the RLR group (53.2 vs. 34.0%; $p = 0.002$) was the only statistically significant difference in baseline characteristics among the two treatment cohorts after PSM.

Intra- and perioperative outcomes

Intra- and perioperative outcomes before and after PSM are depicted in Table 2.

LLR resulted in higher conversion to open approach (8.0 vs 2.1%; $p = 0.042$), higher utilization of Pringle maneuver (50.3 vs 18.1%; $p < 0.001$), lower intraoperative blood loss (median: 150 vs 200 ml; $p < 0.001$), and shorter operative time (210 vs 240 min; $p = 0.049$) compared to RLR before PSM.

Focusing on peri-operative outcomes of pre-PSM populations, RLR resulted in significantly lower hospital stay (median: 4 vs 5 days; $p = 0.008$) compared to LLR, with similar complication rates.

Last, LLR resulted in a higher rate of readmission (7.5 vs 1.1%; $p = 0.020$) and re-interventions (4.8 vs. 0%; $p = 0.022$).

Interestingly, RLR resulted in wider tumor-free margins (median: 10 vs 5 mm; $p < 0.001$) and a higher rate of R0 resection (98.9 vs 91.5%; $p = 0.011$) on postoperative pathology; notably, the RLR group showed a significantly lower prevalence of MVI (24.5 vs 46.5%; $p < 0.001$).

After PSM, RLR was still associated with lower utilization of Pringle (18.1 vs 47.9%; $p < 0.001$), lower conversion rate (2.1 vs 8.5%; $p = 0.039$). longer operative time (240 vs 190 min; $p = 0.002$) and higher blood losses (200 vs 100 ml; $p < 0.001$).

Table 1 Demographic, clinical and treatment characteristics of the study population, before and after propensity score matching

Variable	Level	Before PS matching		*P*-value	SMD	After PS matching		*P*-value	SMD
		Laparoscopic ($N=553$)	Robotic ($N=94$)			Laparoscopic ($N=188$)	Robotic ($N=94$)		
Variables included in PS matching									
Age (y), median (Q1-Q3)		70 (61–76)	65 (57–71)	**<0.001**	0.39	67 (58–72)	65 (57–71)	0.46	0.09
BMI (kg/m^2), median (Q1-Q3)		26 (23–28)	26 (25–30)	**0.013**	0.18	26 (24–29)	26 (25–30)	0.51	0.02
CSPH, N (%)	No	397 (71.8)	47 (50.0)	**<0.001**	0.46	103 (54.8)	47 (50.0)	0.45	0.09
	Yes	156 (28.2)	47 (50.0)			85 (45.2)	47 (50.0)		
AFP (ng/mL), median (Q1-Q3)		9.7 (3.7–74.0)	4.8 (3.3–9.5)	**<0.001**[a]	0.50[a]	5.4 (3.0–16.0)	4.8 (3.3–9.4)	0.66[a]	0.07[a]
Size of principal lesion (mm), median (Q1-Q3)		30 (20–44)	30 (20–40)	0.25	0.13	29 (20–37)	30 (20–40)	0.40	0.07
Number of nodules, N (%)	1	407 (73.6)	89 (94.7)	**<0.001**	0.60	182 (96.8)	89 (94.7)	0.51	0.10
	> 1	146 (26.4)	5 (5.3)			6 (3.2)	5 (5.3)		
Kawaguchi difficulty score, N (%)	1	320 (57.9)	49 (52.1)	0.20	0.19	105 (55.9)	49 (52.1)	0.82	0.08
	2	129 (23.3)	30 (31.9)			57 (30.3)	30 (31.9)		
	3	104 (18.8)	15 (16.0)			26 (13.8)	15 (16.0)		
Variables not included in PS matching									
Gender, N (%)	Male	409 (74.0)	73 (77.7)	0.45	0.09	144 (76.6)	73 (77.7)	0.84	0.03
	Female	144 (26.0)	21 (22.3)			44 (23.4)	21 (22.3)		
CTP Score, N (%)	A	521 (94.2)	85 (90.4)	0.12	0.16	173 (92.0)	85 (90.4)	0.76	0.07
	B	31 (5.6)	8 (8.5)			14 (7.4)	8 (8.5)		
	C	1 (0.2)	1 (1.1)			1 (0.5)	1 (1.1)		
Platelet count, median (Q1-Q3)[b]		165 (110–218)	138 (108–187)	0.059	0.22	145 (96–195)	138 (109–185)	0.98	0.02
Esophageal varices, N (%)[c]	No	426 (82.1)	68 (72.3)	**0.028**	0.23	136 (76.4)	68 (72.3)	0.46	0.09
	Yes	93 (17.9)	26 (27.7)			42 (23.6)	26 (27.7)		
Previous surgery, N (%)	No	332 (60.0)	44 (46.8)	**0.016**	0.27	124 (66.0)	44 (46.8)	**0.002**	0.39
	Yes	221 (40.0)	50 (53.2)			64 (34.0)	50 (53.2)		
Hepatectomy, N (%)	Minor	511 (92.4)	86 (91.5)	0.76	0.03	177 (94.1)	86 (91.5)	0.40	0.10
	Major	42 (7.6)	8 (8.5)			11 (5.9)	8 (8.5)		
Hepatectomy, N (%)	NAR	275 (49.7)	42 (44.7)	0.37	0.10	93 (49.5)	42 (44.7)	0.45	0.10
	AR	278 (50.3)	52 (55.3)			95 (50.5)	52 (55.3)		

Statistically significant *p* values are highlighted with bold and underline

Comparisons between laparoscopic and robotic groups were performed using Wilcoxon signed-rank test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Balance in covariates between treatment groups was also evaluated by standardized mean difference (SMD). A SMD ≤ 0.1 was deemed to be the ideal balance

PS Propensity score, *CSPH* Clinically significant portal hypertension, *AR* Anatomic resection, *NAR* Non-anatomic resection

[a]Evaluated on log-transformed values

[b]75 missing in Laparoscopic group before propensity score matching, 34 missing in Laparoscopic group after propensity score matching

[c]34 missing in Laparoscopic group before propensity score matching, 10 missing in Laparoscopic group after propensity score matching

Nonetheless, the robotic approach resulted in a shorter hospital stay (median: 4 vs 5 days; $p=0.025$) compared to LLR, while the postoperative complication rate was still similar among the two groups.

Focusing on tumor pathology of the PSM population, we confirmed a wider resection margin (median: 10 vs 5 mm; $p=0.002$) and a higher rate or R0 resections (98.9 vs 93.1%; $p=0.037$) following RLR.

Table 2 Outcome variables by type of surgery, before and after propensity score matching

Variable	Level	Before PS matching		*P*-value	After PS matching		*P*-value
		Laparoscopic (*N* = 553)	Robotic (*N* = 94)		Laparoscopic (*N* = 188)	Robotic (*N* = 94)	
Margin (mm), median (Q1-Q3)[a]		5 (2–10)	10 (5–13)	**< 0.001**	5 (2–10)	10 (5–13)	**0.002**
Margin status, N (%)[b]	R0	428 (91.5)	93 (98.9)	**0.011**	161 (93.1)	93 (98.9)	**0.037**
	R1	40 (8.5)	1 (1.1)		12 (6.9)	1 (1.1)	
Microvascular invasion, N (%)[c]	No	253 (53.5)	71 (75.5)	**< 0.001**	97 (64.7)	71 (75.5)	0.075
	Yes	220 (46.5)	23 (24.5)		53 (35.3)	23 (24.5)	
Operation time (min), median (Q1-Q3)		210 (155–290)	240 (180–300)	**0.049**	190 (150–270)	240 (180–300)	**0.002**
Pringle, N (%)	No	275 (49.7)	77 (81.9)	**< 0.001**	98 (52.1)	77 (81.9)	**< 0.001**
	Continue	278 (50.3)	17 (18.1)		90 (47.9)	17 (18.1)	
Conversion open approach, N (%)[d,e]	No	508 (92.0)	92 (97.9)	**0.042**	172 (91.5)	92 (97.9)	**0.039**
	Yes	44 (8.0)	2 (2.1)		16 (8.5)	2 (2.1)	
Intraoperative blood transfusion, N (%)	No	541 (97.8)	86 (91.5)	**0.004**	182 (96.8)	86 (91.5)	0.078
	Yes	12 (2.2)	8 (8.5)		6 (3.2)	8 (8.5)	
Intraoperative mortality, N (%)	No	553 (100)	94 (100)	–	188 (100)	94 (100)	–
	Yes	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Blood loss (mL), median (Q1-Q3)[f]		150 (50–290)	200 (100–400)	**< 0.001**	100 (50–250)	200 (100–400)	**< 0.001**
Length of hospital stay (day), median (Q1-Q3)[g]		5 (4–6)	4 (3–6)	**0.008**	5 (4–6)	4 (3–6)	**0.025**
Postoperative blood transfusion, N (%)	No	528 (95.5)	89 (94.7)	0.79	184 (97.9)	89 (94.7)	0.17
	Yes	25 (4.5)	5 (5.3)		4 (2.1)	5 (5.3)	
Clinically-relevant complication, N (%)	No	531 (96.0)	90 (95.7)	0.78	183 (97.3)	90 (95.7)	0.49
	Yes	22 (4.0)	4 (4.3)		5 (2.7)	4 (4.3)	
In-hospital mortality, N (%)	No	552 (99.8)	94 (100.0)	1.00	188 (100)	94 (100)	–
	Yes	1 (0.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Re-admission, N (%)[h]	No	443 (92.5)	93 (98.9)	**0.020**	148 (95.5)	93 (98.9)	0.26
	Yes	36 (7.5)	1 (1.1)		7 (4.5)	1 (1.1)	
Re-intervention, N (%)[i]	No	458 (95.2)	94 (100.0)	**0.022**	152 (97.4)	94 (100.0)	0.30
	Yes	23 (4.8)	0 (0.0)		4 (2.6)	0 (0.0)	

Statistically significant *p* values are highlighted with bold and underline

Comparisons between laparoscopic and robotic groups were performed using Wilcoxon signed-rank test for continuous variables and Chi-square test or Fisher's exact test for categorical variables

PS propensity score, *mm* millimeter, *min* minutes, *mL* milliliter

[a]85 missing in Laparoscopic group before propensity score matching, 15 missing in Laparoscopic group after propensity score matching

[b]85 missing in Laparoscopic group before propensity score matching, 15 missing in Laparoscopic group after propensity score matching

[c]80 missing in the Laparoscopic group before propensity score matching, 38 missing in the Laparoscopic group after propensity score matching

[d]1 missing in the Laparoscopic group before propensity score matching

[e]Reasons for conversion in 44 out of 533 LLR before PSM: Oncologic purposes (n=20), Hemorrhage (n=11), Adhesions (n=10), Visceral or vascular lesions (n=2), Biliostasis (n=1); reasons for conversion in 2 out of 94 RLR before PSM: Oncologic purposes (n=1), Anesthesiologic issues (n=1); reasons for conversion in 16 out of 188 LLR after PSM: Oncologic purposes (n=5), Hemorrhage (n=5), Adhesions (n=5), Visceral or vascular lesions (n=1)

[f]2 missing in Laparoscopic group before propensity score matching, 1 missing in Laparoscopic group after propensity score matching

[g]2 missing in Laparoscopic group before propensity score matching

[h]74 missing in Laparoscopic group before propensity score matching, 33 missing in Laparoscopic group after propensity score matching

[i]72 missing in Laparoscopic group before propensity score matching, 32 missing in Laparoscopic group after propensity score matching

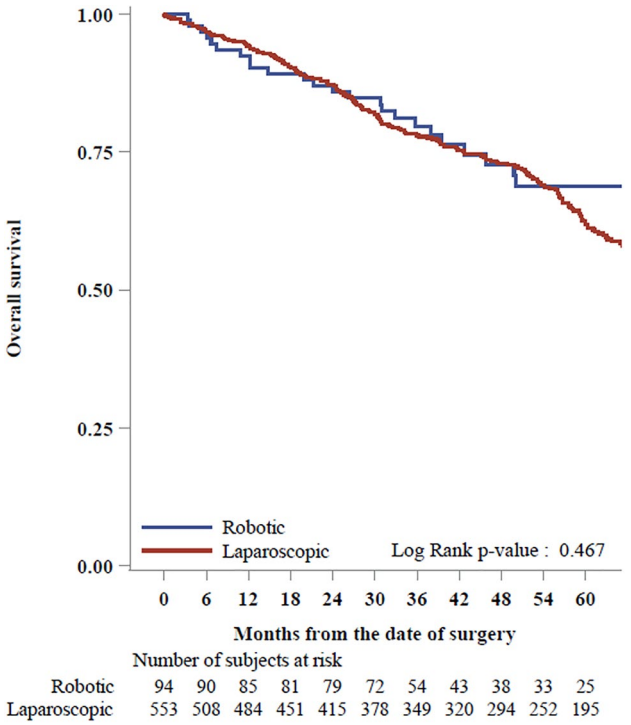


Fig. 1 Overall survival before propensity score matching, by surgical technique (Median FU (Q1-Q3) in months: 50 (25-65))

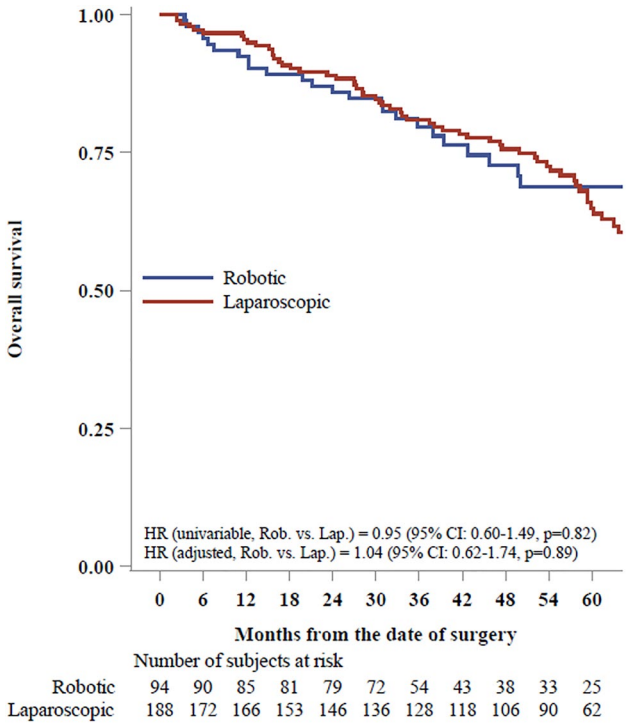


Fig. 3 Overall survival after propensity score matching, by surgical technique (Median FU (Q1-Q3) in months: 50 (29-64))

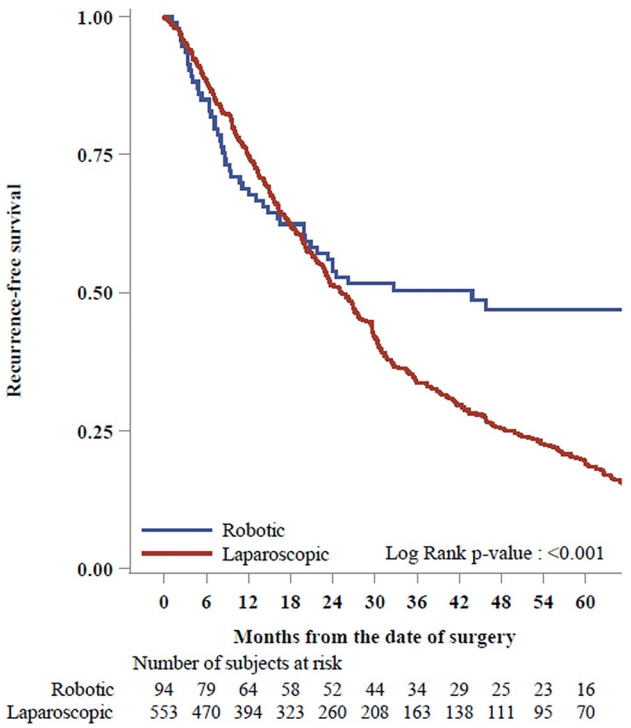


Fig. 2 Recurrence-free survival before propensity score matching, by surgical technique

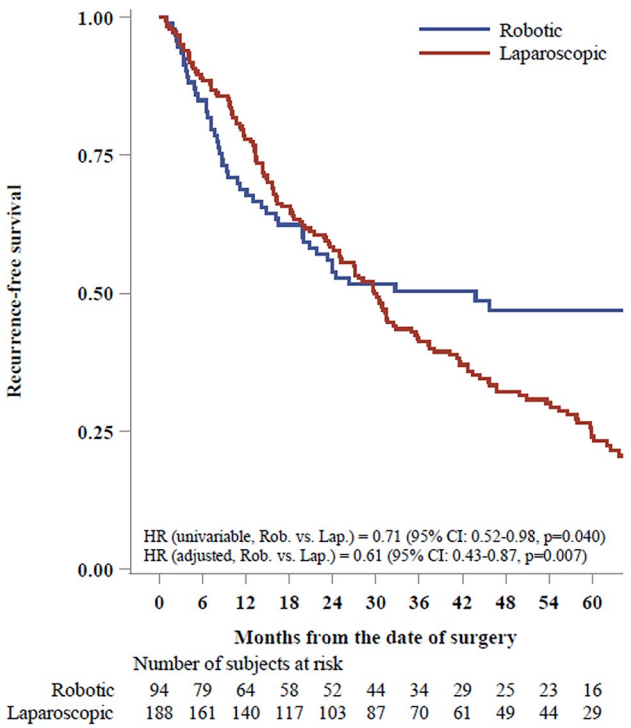


Fig. 4 Recurrence-free survival after propensity score matching, by surgical technique

Oncologic outcomes

Median follow-up lasted 50 (IQR: 25–65) months.

Focusing on pre-PSM population we highlighted similar 5-year OS following RLR and LLR (68.7 vs 61.8%; $p = 0.47$) (Figure 1), while RLR resulted in significantly higher RFS (5-y RFS: 46.8 vs 18.9%; $p < 0.001$) (Figure 2).

After PSM, OS remained similar among RLR and LLR cohorts [5-y OS: 68.7 vs 65.0%; univariable HR = 0.95 (95% CI: 0.60–1.49); $p = 0.82$] (Figure 3), with significantly better RFS in RLR cohort [5-y RFS: 46.8 vs 24.0%; univariable HR = 0.71 (95% CI: 0.52–0.98); $p = 0.04$] (Figure 4).

After adjusting the HR estimates for covariates with SMD > 0.1 in the post-PSM cohort, the OS-adjusted HR following RLR was 1.04 (95% CI: 0.62–1.74, $p = 0.89$), with a RFS adjusted HR of 0.61 (95% CI: 0.43–0.87, $p = 0.007$).

Discussion

Minimally invasive liver surgery (MILS) in an HCC setting has experienced striking development and worldwide diffusion over the last decades, and its clinical advantages over OLR have become widely acknowledged [6, 7, 11, 12].

Despite that, comparisons between LLR and RLR techniques are relatively scarce and partially discordant [20–26], although there is emerging evidence concerning the potential advantages of RLR over LRR: in particular RLR seems to provide lower conversion rates in challenging resections [33] compared to LLR, and could potentially enhance the successful implementation of MILS in these settings.

Given this background, we sought to compare perioperative and oncologic outcomes of RLR and LLR in a multicentric, PSM population of HCC patients included in the IGoMILS registry.

Considering their potential effect on surgical indication and overall prognosis, patient age, BMI, CSPH, number of nodules, size of the principal lesion, αFP and Kawaguchi difficulty score were all entered into the PSM model to grant a weighted comparison of the two treatment cohorts.

Looking at baseline characteristics of the study population, we should acknowledge a non-negligible proportion (203/647: 31.4%) of HCC patients with signs of CSPH undergoing curative-intent resection (regardless of the chosen approach): such data strengthens the role of MILS as a pivotal driver towards the expansion of surgical indications in cirrhosis setting, as recently suggested form several Authors [11, 12]. Moreover, the relatively high patient age supports the beneficial effect of MILS in the elderly, as pointed out by other research groups [34].

Focusing on the post-PSM population, we could notice a good balancing of preoperative characteristics among the two cohorts, although the LLR population presented a significantly higher rate of R1 resection and generally closer tumor-free margins on resected specimen – the prognostic implications of such mismatches will be further discussed.

The primary study endpoint focused on the comparison of perioperative outcomes following LLR and RLR.

Concerning intraoperative outcomes, we highlighted lower conversion rate in the RLR cohort both before and after PSM: such result probably relies on easier management of intraoperative bleedings thanks to instrument flexibility and increased dexterity of the robotic platform, that facilitates suturing and knotting [35], and therefore bleeding control. Notably, neither of the two open conversions in the RLR group was due to intraoperative hemorrhage, whereas in the LLR group, 11 out of 44 conversions were prompted by intraoperative bleeding.

Interestingly, we also observed a relatively higher median blood loss in the RLR group compared to LLR. A plausible explanation is that significant intraoperative bleedings during RLR were predominantly managed without conversion, ultimately leading to greater blood loss in this cohort. However, despite this statistically significant difference, the increased blood loss did not translate into higher transfusion rates or a greater need for open conversion (as previously discussed), suggesting no real clinical impact. Interestingly, this discrepancy was also noted in a recent study comparing robotic and open resection in an HCC setting [19], where the increased intraoperative bleeding in the robotic group similarly did not result in a higher transfusion rate. We hypothesize that the lower utilization of the Pringle maneuver observed in the robotic cohort, as well as the more frequent application of CUSA technology in the laparoscopic setting, may have contributed to the increased blood loss during RLR. Additionally, it is important to consider that the estimation of intraoperative blood loss in hepato-pancreato-biliary surgery has recently been re-evaluated [36], revealing significant variability in measurement across existing literature. Therefore, the consistency of these data might be influenced by different estimation and recording practices across the 12 participating centers.

As previously mentioned, RLR was also associated with a higher rate of R0 resections and wider resection margins both pre- and post-PSM: while such result does not seem to rely on different surgical planning—Kawaguchi difficulty score was comparable among groups—we could hypothesize how increased dexterity of robotic arms and utilization of indocyanine green fluorescence for intraoperative navigation could have played a role in enhancing R0 resection (i.e. allowing a safer dissection close to major vessels) [37]. Notably, our data did not highlight any significant difference towards the application of anatomical vs. non-anatomical or major vs. minor liver resections among the RLR and LLR cohorts; while the oncologic benefit of anatomical resections in the HCC setting is still debated [38], recent evidence

suggests that wider margins could play a more important role in determining postoperative recurrence [39]. In conclusion, higher R0 resection rates and wider resection margins of the RLR cohort might have played a role in the different recurrence rate highlighted in our study, as we will further discuss.

Focusing on perioperative outcomes, we should acknowledge how both techniques resulted in a favorable postoperative course: in fact, major morbidity rate (Clavien-Dindo ≥ 3) and perioperative mortality was comparable to those reported in other large MILS series [40] and did not significantly differ among LLR and RLR cohorts. Conversely, hospital stay seemed shorter following RLR both before and after PSM: once again, although statistically significant, this result should be cautiously discussed.

On one hand, the significantly older patient age in the LLR cohort (pre PSM) could have played a role in postoperative recovery, but such discrepancy might have been counterbalanced by the relatively higher prevalence of CSPH in the RLR cohort. Beside such speculations, we should point out how RLR resulted in a shorter length of stay even after PSM, although such discrepancy could still rely on different center policies according to chosen approach.

As a secondary outcome, we sought to analyze the oncologic results following RLR and LLR: RFS was significantly better after RLR both before and after PSM, with a similar OS both pre- and post-PSM populations.

MVI is widely recognized as one of the most significant risk factors for early HCC recurrence following resection and transplantation [41, 42]. Notably, we highlighted a significantly higher prevalence of MVI in the pre-PSM LLR cohort. While this could have contributed to the higher recurrence rates, the absence of a centralized pathology review represents a potential limitation when assessing the true impact of MVI on oncologic outcomes.

After PSM, MVI distribution was no longer statistically different between the two groups, mitigating its potential confounding effect. Additionally, MVI—along with other covariates with an SMD > 0.1—was accounted for in the HR evaluation of the post-PSM cohort.

However, other unbalanced variables (e.g., presence of satellite nodules, MELD score), which were either unavailable in the database or not fully accounted for by the PSM process, could have also influenced the results. For instance, given the study timeframe for patient enrollment, it is likely that several centers were in the early stages of their learning curve for robotic liver resection: we cannot exclude the possibility that these patients underwent a "super-selection" process, which may have subtly yet significantly impacted the oncologic outcomes.

As previously discussed, RLR resulted in a higher rate of R0 resections and wider resection margins, likely reducing tumor recurrence by addressing microsatellite disease surrounding the main nodule.

The improved RFS observed in the RLR group may, therefore, be attributed, at least in part, to the advantages of the robotic platform: tremor filtration, motion scaling, and magnified 3-dimensional vision directly contribute to increased precision and better dissection and could play a role in enhancing R0 resection (i.e. allowing a safer dissection close to major vessels) with direct impact on oncologic results.

Interestingly, a recent multicenter study reported a similar improvement in RFS following robotic versus open liver resections [19]. This finding was further supported by a more recent single-center analysis specifically comparing robotic and laparoscopic resections in HCC [43].

Despite a better RFS in the RLR group, OS was similar in the pre- and post-PSM populations. It is important to point out that we did not account for recurrence patterns (solitary, multifocal, intrahepatic, extrahepatic, mixed etc.) or treatment strategies of recurrences (transplantation, redo surgery, ablative techniques, endo-arterial treatments, systemic treatment), that could have a direct impact on post-recurrence survival, but whose analysis was not among the study endpoints. As a result, the potential impact of post-recurrence interventions on OS cannot be fully accounted for in our analysis, and this introduces a limitation when interpreting the OS findings. For the same reason, we should acknowledge that surgical technique – aside from perioperative mortality, which was comparable between the two cohorts– plays a limited role on the determination of long-term patient prognosis. Consequently, OS is of lesser relevance in the context of this technical comparison.

In summary, the actuarial oncologic benefit of robotic over laparoscopic resection for HCC should be better evaluated in larger prospective series to drive stronger conclusions.

This study presents several limitations. First, its retrospective nature implies selection and indication biases. Second, its multicentric design could imply different patient management and potentially affect the comparison of perioperative outcomes. Third, not all centers had access to the robotic platform simultaneously or throughout the entire study period. To mitigate potential treatment allocation bias (LLR vs RLR), we incorporated the Kawaguchi difficulty score in the propensity score matching (PSM). Fourth, data from the IGoMILS registry did not include tumor location and relation to major vessels and therefore we were obliged to select the Kawaguchi difficulty score rather than other scores (i.e. Iwata) that have been validated in the RLR setting [44, 45]. Last, we were not able to provide any comparison concerning surgical costs.

In conclusion, both LLR and RLR granted good postoperative outcomes with excellent morbidity and mortality rates,

despite a relatively old patient age and significant prevalence of CSPH in the study population.

Thanks to the specific characteristics of the robotic platform, RLR seemed to enhance intraoperative bleed management resulting in lower conversion rates. Moreover, hospital stay was significantly shorter following RLR, even though such results may rely on different patient management across participating centers. Focusing on oncologic outcomes, we highlighted a significantly better RFS after RLR, probably related to the higher rate of R0 resection with wider tumor-free margins in the RLR cohort. The results of this retrospective multicentric analysis should be hopefully implemented through large prospective randomized clinical trials.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13304-025-02293-z.

Acknowledgements The authors would like to thank the MODENA ARTS FOUNDATION for its support of scientific research and for its contribution to the development of this study. IGoMILS Collaborative Group: Giorgio Ercolani, Matteo Ravaioli, Andrea Belli, Matteo Barabino, Alberto Brolese, Giovanni Vennarecci, Antonio Frena, Giorgio Rossi, Riccardo Memeo, Ugo Boggi, Giacomo Batignani, Mohammed Abu Hilal, Gian Luca Grazi, Leonardo Vincenti, Guido Griseri, Marco Massani, Luca Morelli, Fulvio Calise, Raffaele Romito, Fausto Zamboni, Guido Torzilli, Marco Filauro, Stefano Berti, Marco Vivarelli, Giuseppe Navarra, Giuseppe Tisone, Amedeo Carraro, Andrea Coratti, Graziano Ceccarelli, Christian Cotsoglou, Daniela Caracciolo, Giulio Belli, Pietro Mezzatesta, Adelmo Antonucci, Luigi Veneroni, Dario Lorenzin, Albero Patriti, Michele Colledan, Amilcare Parisi, Francesco Coratti, Anna Lucia Segreto, Silvio Guerriero, Marco Spada, Stefano Mancini, Marcello Spampinato, Antonio Floridi, Giovanni Sgroi, Fabrizio Romano, Paola Tarchi, Dario Ribero, Pietro Maida, Luigi Boni, Andrea Percivale, Umberto Montin

Data availability The data of current study is available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests, financial or non-financial, directly or indirectly related to the work submitted for publication. No specific funding was received for this study.

Ethical approval This study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Given the retrospective nature of the analysis, informed consent was not required.

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