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Laparoscopic liver resection of hepatocellular carcinoma located in unfavorable segments: a propensity score-matched analysis from the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) Registry

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Abstract

Objective Laparoscopic liver resection (LLR) for Hepatocellular Carcinoma (HCC) is one of the most important indications for the minimally invasive approach. Our study aims to analyze the experience of the Italian Group of Minimally Invasive Liver Surgery with laparoscopic surgical treatment of HCC, with a focus on tumor location and how it affects morbidity and mortality.

Methods 38 centers participated in this study; 372 cases of LLR for HCC were prospectively enrolled. Patients were divided into two groups according to the HCC nodule location. Group 1 favorable location and group 2 unfavorable location. Perioperative outcomes were compared between the two groups before and after a propensity score match (PS) 1:1.

Results Before PS in group 2 surgical time was longer; conversion rate was higher; postoperative transfusion and comprehensive complication index were also higher. PS was performed with a cohort of 298 patients (from 18 centers), with 66 and 232 patients with HCC in unfavorable and favorable locations, respectively. After PS matching, 62 patients from group 1 and group 2 each were compared. Operative and postoperative course were similar in patients with HCC in favorable and unfavorable LLR locations. Surgical margins were found to be identical before and after PS.

Conclusions These results show that LLR in patients with HCC can be safely performed in all segments because of the extensive experience of all surgeons from multiple centers in performing traditional open liver surgery as well as laparoscopic surgery.

Keywords Laparoscopic HCC · Posterior segment · Hepatocellular carcinoma · IGoMILS · Child B · Laparoscopic liver resection

Hepatocellular carcinoma (HCC) is the fifth most common primary cancer and the second and sixth most common cause of cancer-related deaths worldwide in males and females, respectively [1]. Surgical resection is a potential curative treatment for patients with HCC [2]. Minimally invasive approaches for liver resection have considerably improved since the First International Consensus Conference on Laparoscopic Liver Resection (LLR) (Louisville 2008) [3]. Laparoscopic segments and minor LLRs should be a standard practice. In 2014 in Morioka, it was concluded that major LLR is still in exploratory or learning phase and has undefined risks [4]. LLR for patients with HCC has confirmed the theoretical benefits of the laparoscopic approach, such as reduced parietal and hepatic injury, preserved collateral venous circulation, and decreased rates of postoperative liver failure and ascites. Here, we aim to analyze the experience of the Italian Group of Minimally Invasive Liver Surgery (IGoMILS) with laparoscopic surgical treatment of

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HCC, with a focus on tumor location and how it affects morbidity and mortality.

Methods

Since November 2014, all cases of LLR have been prospectively registered. All Italian centers had the opportunity to participate in this project. We analyzed all cases of HCC resection registered from November 2014 to August 31, 2016. Thirty-eight centers participated in this study; 372 cases of LLR for HCC were enrolled. Patient characteristics and surgical and perioperative data, including duration of surgery, estimated blood loss, length of postoperative hospital stay, types of complications, and other variables, were obtained from the database.

HCC nodule location was defined as a favorable location in case of anterolateral segments 2, 3, 4b, 5, and 6 and as an unfavorable location in case of posterior superior Couinaud segments 1, 4a, 7, and 8. Major hepatectomy was defined as resection of three or more Couinaud segments. Portal hypertension was defined as portal venous pressure of > 10 mmHg, presence of portosystemic collateral vessels, or the presence of esophageal varices.

Patients were divided into two groups on the basis of HCC nodule location. Group 1 (favorable location) included patients with HCC nodule on laparoscopic segments and group 2 (unfavorable location) included patients with HCC nodule on non-laparoscopic segments. Postoperative complications were defined according to the comprehensive complication index (CCI) [5]. Patients in group 1 were matched at a ratio of 1:1 with patients who had undergone resection in group 2. The matching was achieved on the basis of propensity scores (PSs), including the following eight covariables: sex, age, body mass index (BMI), Model for End-Stage Liver Disease (MELD), Child-Pugh Score (Child), previous cholecystectomy, type of liver parenchyma, nodule diameter. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, and this study was approved by the institutional review board.

Propensity score matching

PS matching was performed on the cohort to adjust any difference in average outcomes for segment location selection bias. PS matching was performed by considering all significant variables between the two groups in the preliminary analysis. PSs were generated by logistic regression and relied on the following covariables: sex, age, BMI, MELD, Child, previous cholecystectomy, type of liver parenchyma, and nodule diameter. After estimation of PSs, a regular 1:1 nearest-neighbor matching process was performed. A small caliper (0·1) was specified to improve balance.

Statistical analysis

A 1:1 PS matching was performed between group 1 and group 2 to minimize selection bias in the baseline characteristics between the two groups of patients. A logistic regression model was used to estimate PS for a patient who underwent LLR for an anterolateral nodule to match with a patient who underwent LLR for a posterolateral nodule.

All variables were compared using the χ^2 or Fisher's exact test for categorical data, the Mann–Whitney *U*-test for non-normally distributed continuous data, and the Student's *t*-test for normally distributed continuous variables. All data are expressed as mean ± standard deviation or median and range. A p value of < 0.05 was considered as statistically significant. Statistical analyses were performed using the SPSS Statistics version 21.0 (IBM SPSS).

Results

A total of 378 patients who underwent LLR for HCC were enrolled from 38 Italian centers. Group 1 comprised 306 patients; group 2 comprised 66 patients. In the first group, nodules were in segment II in 49 cases, in segment III in 69 cases, in segment IVb in 33 cases, in segment V in 62 cases, and in segment VI in 93 cases. In group 2, nodules were in segment: I in 3 cases, IVa in 16 cases, VII in 28 cases, and in VIII in 19 cases.

Before matching the two groups, no differences were observed regarding sex, age, BMI, clamping time, number of nodules, Edmondson grade, vascular infiltration, Classification of Malignant Tumours (TNM), previous cholecystectomy, alphafetoprotein, portal hypertension, nodule diameter, surgical margin, estimated blood loss, intraoperative transfusion, and the length of hospital stay. On the other hand, there were more Child B in the laparoscopic group (21 vs. 0; $p = 0.008$), and the MELD score was higher in group 1 (8 vs. 7; $p = 0.021$). Surgical time was longer in group 2 (180 min vs. 240 min, $p < 0.001$); conversion rate was higher in group 2 (5% vs. 18%; $p < 0.001$). Postoperative transfusion and CCI were also greater in group 2 ($p = 0.027$; $p < 0.001$). Results are further provided in Table 1.

Portal hypertension was observed in 109 patients, of whom 93 (85.3%) were in group 1 and 16 (14.7%) in group 2.

PS was performed with a cohort of 298 patients (from 18 centers), with 66 and 232 patients with HCC in unfavorable and favorable locations, respectively. After PS matching, 62 patients from group 1 and group 2 each

Table 1 First analysis of the 372 cases

	Group 1 Anterior segment	Group 2 Posterior segment	*p* value
Cases	312	66	
Gender (male/female)	214/92	54/12	0.051
Age median (IQR)	70 (62–76)	71 (61–75)	0.810
BMI (IQR)	25 (22–28)	26 (24–28)	0.393
Alpha fetoprotein			0.489
Child (A/B)	263/29	65/0	**0.008**
MELD (IQR)	8 (7–9)	7 (6–8)	**0.021**
Pringle (0/1/2/3)	5/207/74/2	0/39/22/2	**0.023**
Clamping time (IQR)	39.5 (20.5–60.5)	30 (15–45)	0.419
Number nodule (0/1/2/3/4/5/6)	2/258/23/6/3/2/0	0/55/7/2/0/0/1	0.368
Edmonson grade			0.620
Vascular infiltration (no/yes)	189/104	41/24	0.829
TNM (0/1/2/3)	4/157/108/20	0/34/26/3	0.913
Previous cholecystectomy (no/yes)	275/31	59/7	0.908
Parenchyma (0/1/2/3/4)	1/17/12/68/208	0/6/3/25/32	**0.024**
Portal hypertension (no/yes)	212/93	50/16	0.352
Nodule diameter (mm) (IQR)	30 (20–40)	30 (20–45)	0.891
Margin (mm) (IQR)	5 (0–10)	5 (0–10)	0.347
Surgical time (min) (IQR)	180 (120–240)	240 (172–300)	**0.001**
Type of resection			**0.001**
Wedge	140	33	
Segmentectomy	116	13	
Left lateral sectionectomy	31	1	
Right posterior bisegm.	1	2	
Right anterior bisegm.	–	1	
Bisegmentectomy	11	2	
Right hepatectomy	3	6	
Left hepatectomy	9	6	
Central hepatectomy	1	–	
ALPPS 1° step	–	1	
ALPPS 2° step	–	1	
Blood loss	110 (50–250)	200 (50–300)	0.256
Conversion	270/17	51/12	**0.001**
Bleeding	8	4	0.159
Adherence syndrome	3	2	0.197
Oncological radicality	7	5	**0.029**
Biliary stasis	1	2	**0.027**
Anesthesia	0	1	**0.032**
Intraoperative transfusion	9	5	0.076
Post-operative transfusion	62	22	**0.027**
Comprehensive complication index	4.38	7.70	**0.001**
Length of stay (days)	5 (4–6)	5 (3–7)	0.110

Bold values indicate statistical significance at $p < 0.05$

Parenchyma (0 = not available; 1 = healthy; 2 = steatosis; 3 = chronic hepatitis; 4 = cirrhosis); pringle (0 = not available; 1 = not performed; 2 = intermittent: 3 = continuous)

were compared (Fig. 1). Surgical findings such as nodule diameter ($p = 0.677$), margin resection ($p = 0.283$), surgical time ($p = 0.438$), type of resection ($p = 0.063$), estimated blood loss ($p = 0.966$), and intraoperative transfusion ($p = 0.499$) were similar between the two groups. The rate of conversion to open surgery ($p = 0.041$) was

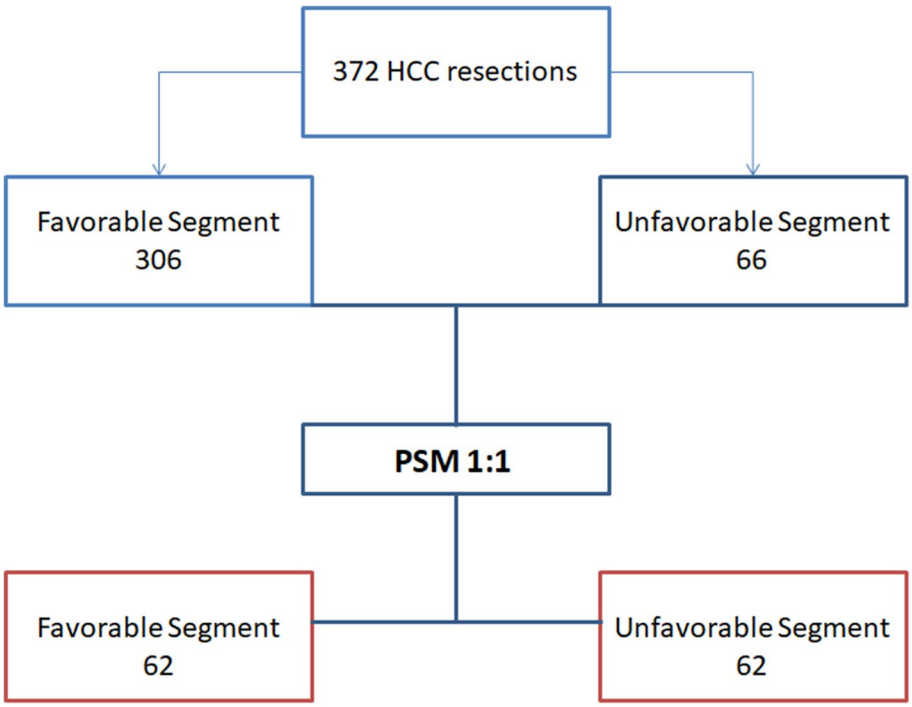

Fig. 1 Flow diagram of propensity score

higher in the unfavorable group. Postoperative morbidity was similar for postoperative transfusion ($p=0.143$), CCI ($p=0.061$) and the length of hospital stay ($p=0.112$). All results after matching are provided in Table 2. We analyzed the contributions of 38 centers to control potential bias. Eighteen centers enrolled 66 and 232 patients with HCC in unfavorable and favorable (74.3% of group 1) locations, respectively. Only patients from these 18 centers were considered for PS.

Discussion

The present study reports the results of a prospective multicentric study of LLR for patients with HCC before and after PS matching. Operative and postoperative course were similar in patients with HCC in favorable and unfavorable LLR locations. Pre-matching analysis revealed some differences between LLR for patients with HCC in favorable and unfavorable locations. Preoperative differences were observed in the MELD score and Child score. Surgical time was greater in HCC in group 2 ($p=0.001$). Conversion rate was higher in group 2 ($p=0.001$), particularly for oncological radicality, biliary stasis, and anesthesia-related concerns. postoperative transfusion and CCI ($p=0.001$) were higher in group 2. These results suggest that LLR for patients with HCC in unfavorable locations is more complicated than that in favorable locations. Careful PS matching did not confirm the previous differences between the groups. Preoperative, surgical, and postoperative characteristics were similar between the groups (Table 2). Surgical time ($p=0.438$) and morbidity ($p=0.061$) were also similar between the groups. Surgical margins were found to be similar after the first analysis ($p=0.347$) and PS matching ($p=0.283$). These data support the use of PS matching, which contradicts the current thinking that laparoscopy does not provide an oncologically adequate margin for the unfavorable locations. This is an imperative finding with respect to LLR of HCC. The Louisville consensus conference [3] and Morioka [4] recommended the resection of anterior segments only and referring the resection of lesions in the posterior segments to specialized centers. The Southampton Guidelines (2017) confirmed the previous statement and recommended that patients with HCC or cirrhotic liver should be referred to specialized centers [6].

We also want to acknowledge the participation of the 38 centers in this study, of which 18 have reported at least one patient in the group of patients with HCC in unfavorable locations (Table 3). The prevalence of LLR in many Italian centers is growing; many of them use laparoscopy in cases of HCC in unfavorable locations and have obtained good outcomes.

Furthermore, in our series, 29 patients were classified as Child B. Tumor localization of this subgroup of patients was in the laparoscopic segments (segment 2 in two cases, segment 3 in 11 cases, segment 4b in three cases, segment 5 in five cases, and segment 6 in eight cases). Only one patient underwent a major hepatectomy; others were treated with minor resections. Moreover, 109 patients had portal hypertension with 16 cases in group 2 and 93 in group 1.

Table 2 After propensity score matching, using cases of the 18 centers unrolling patient in both groups

	Group 1 Anterior segment	Group 2 Posterior segment	*p* value
Cases	62	62	1
Gender	48/14	50/12	0.662
Age	68 (58–73)	71 (59.5–75)	0.383
BMI	24 (20–28.5)	25 (22.5–27)	0.964
MELD	7 (6–8)	7 (6–8)	0.108
Pringle	19	23	0.195
Clamping time	55 (27–65.5)	32.5 (18–45)	0.425
Nodule (1/2/3/4/5/6)	52/7/3/0/0/0	52/7/2/0/0/1	0.499
Previous cholecystectomy	9	6	0.413
Parenchyma (1/2/3/4)	6/5/20/31	5/2/24/31	0.628
Portal hypertension (no/yes)	44/18	47/15	0.546
Nodule diameter	30.5 (25–45)	30 (20–45)	0.677
Margin	7 (2–10)	5 (0–10)	0.283
Surgical time	238 (150–300)	240 (168.5–300)	0.438
Type of resection			0.063
Wedge	28	32	
Segmentectomy	24	12	
Left lateral sectionectomy	5	–	
Right posterior bisegm.	–	4	
Bisegmentectomy	4	2	
Right hepatectomy	1	7	
Left hepatectomy	–	5	
Blood loss	150 (50–300)	200 (75–300)	0.966
Conversion	59/3	51/11	**0.041**
Bleeding	3	4	0.734
Adherence syndrome	0	2	0.164
Oncological radicality	1	4	0.186
Biliary stasis	0	2	0.164
Anesthesia	0	1	0.328
Intraoperative transfusion	3	5	0.499
Post-operative transfusion	2	6	0.143
Comprehensive complication index	4.2	8.6	0.061
Length of stay	4 (3–5)	5 (3–7)	0.112

Analysis on 62 cases for each groups. Parenchyma (0 = not available; 1 = healthy; 2 = steatosis ; 3 = chronic hepatitis ; 4 = cirrhosis); pringle (0 = not available; 1 = not performed; 2 = intermittent: 3 = continuous)

The results are in parallel with those of the abovementioned Child B.

The LLR ‘‘success’’ was first based on the concept appropriate patient, with appropriate disease treated at the appropriate center. Nevertheless, many studies on LLR for patients with HCC are available. Most of these studies compare open surgery with laparoscopic approach with respect to minor resections, major resections, and cases of HCC in unfavorable locations. The minimal invasive approach has contributed to expand the indication for LLR for patients with HCC without increasing the incidence of perioperative morbidity [7]. Moreover, many studies have compared the results of LLR with those of open liver resection for HCC without finding differences or better yet improving short-term outcomes [8, 9]. Techniques for laparoscopic approaches for lesions in the deep segments of the liver were originally described by Gayet [10]. LLR has been reported as feasible for all liver segments with acceptable morbidity [11, 12]. In this way, other studies confirmed the possibility of expanding the use of LLR for HCC in unfavorable locations. Recent improvements in surgical techniques and accumulated experience allow surgeons to perform resection of HCC in segments 7 and 8 [13, 14] as well as the right anterior sectionectomy [15] or the right posterior sectionectomy [16]. Besides, major resection such as right hepatectomy has been reported to

Table 3 Number of cases of the 18 centers unrolling unfavorable cases

Center	Cases	Unfavorable cases
1	59	13
4	5	2
6	26	5
9	7	2
13	15	5
16	6	1
17	29	9
18	20	2
20	6	3
21	41	8
28	14	2
29	7	1
30	17	7
34	10	1
35	11	1
45	1	1
47	20	2
51	4	1

be safe in selected patients and represents a viable alternative to the traditional approach [17–19].

Some previous limitations for LLR indication seem to have been overpassed recently. Patient age [20] and tumor size [21] are no longer the limitations for LLR in patients with HCC [22, 23]. More recently, cirrhosis has been proposed as an extended indication for LLR in patients with HCC [24, 25].

The present results are from an Italian multicentric study comparing LLR before and after the implementation of PS matching in patients with HCC localized in favorable or unfavorable locations. The inclusion of a large number of hepatectomies in both groups permitted a high degree of PS matching. Concerning the number of patients with HCC localized in the unfavorable locations, we observed a good balance between all enlistment centers. These results show that LLR in patients with HCC can be safely performed in all segments because of the extensive experience of all surgeons from multiple centers in performing traditional open liver surgery as well as laparoscopic surgery.

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Compliance with ethical standards

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