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ORIGINAL ARTICLE

The largest western experience on salvage hepatectomy for recurrent hepatocellular carcinoma: propensity score-matched analysis on behalf of He.RC.O.Le.Study Group

Maurizio Iaria[1], Giorgio Bianchi[1], Federico Fazio[2], Francesco Ardito[3], Pasquale Perri[4], Nicholas Pontarolo[5], Simone Conci[6], Matteo Donadon[7,8], Matteo Zanello[9], Quirino Lai[10], Simone Famularo[7,8,11], Sarah Molfino[12], Ivano Sciannamea[13], Luca Fumagalli[14], Paola Germani[15], Antonio Floridi[16], Cecilia Ferrari[17], Giuseppe Zimmitti[18], Albert Troci[19], Mauro Zago[14,20], Valentina Ferraro[21], Federica Cipriani[22], Stefan Patauner[23], Giuliano La Barba[24], Maurizio Romano[25], Giacomo Zanus[25], Giorgio Ercolani[24,26], Antonio Frena[23], Luca Aldrighetti[22], Riccardo Memeo[21], Enrico Pinotti[20], Michele Crespi[19], Moh'd Abu Hilal[18], Guido Griseri[17], Paola Tarchi[15], Marco Chiarelli[14], Adelmo Antonucci[13], Gian L. Baiocchi[12], Fabrizio Romano[11,27], Massimo Rossi[10], Elio Jovine[9], Guido Torzilli[7,8], Andrea Ruzzenente[6], Marcello Maestri[5], Gian L. Grazi[4], Felice Giuliante[3], Alessandro Ferrero[2], Raffaele Dalla Valle[1] HE.RC.O.LE.S. GROUP

[1]Department of General and Specialized Surgery, Division of General Surgery, Parma University Hospital, Parma, [2]Department of HPB and Digestive Surgery, Ospedale Mauriziano Umberto I, Turin, [3]Hepatobiliary Surgery Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, [4]Division of Hepatobiliarypancreatic Surgery, IRCCS - Regina Elena National Cancer Institute, Rome, [5]Unit of General Surgery 1, University of Pavia and Foundation IRCCS Policlinico San Matteo, Pavia, [6]Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, [7]Department of Biomedical Science, Humanitas University, Pieve Emanuele, [8]Department of Hepatobiliary and General Surgery, IRCCS Humanitas Research Hospital, Rozzano, Milan, [9]Department of Surgery, AOU Sant'Orsola Malpighi, IRCCS, Bologna, [10]General Surgery and Organ Transplantation Unit, Sapienza University of Rome, Umberto I Polyclinic of Rome, Rome, [11]School of Medicine and Surgery, University of Milano-Bicocca, Monza, [12]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, [13]Department of Surgery, Monza Policlinic, Monza, [14]Department of Emergency and Robotic Surgery, ASST Lecco, Lecco, [15]Department of General Surgery, ASUGI, University Hospital of Trieste, Trieste, [16]Department of General Surgery, ASST Crema, Crema, [17]HPB Surgical Unit, San Paolo Hospital, Savona, [18]Department of Surgery, Fondazione Poliambulanza - Istituto Ospedaliero, Brescia, [19]Department of Surgery, L. Sacco Hospital, Milan, [20]Department of Surgery, Ponte San Pietro Hospital, Bergamo, [21]Department of Hepato-Pancreatic-Biliary Surgery, Miulli Hospital, Bari, [22]Hepatobiliary Surgery Division, Ospedale San Raffaele, Milano, [23]Department of Surgery, Bolzano Central Hospital, Bolzano, [24]General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Forlì, [25]Department of Surgical, Oncological and Gastroenterological Science (DISCOG), University of Padua, Hepatobiliary and Pancreatic Surgery Unit - Treviso Hospital, Treviso, [26]Department of Medical and Surgical Sciences, University of Bologna, Italy, and [27]Department of Surgery, San Gerardo Hospital, Monza

Abstract

Background: We aimed to evaluate, in a large Western cohort, perioperative and long-term oncological outcomes of salvage hepatectomy (SH) for recurrent hepatocellular carcinoma (rHCC) after primary hepatectomy (PH) or locoregional treatments.

Methods: Data were collected from the Hepatocarcinoma Recurrence on the Liver Study Group (He.RC.O.Le.S.) Italian Registry. After 1:1 propensity score-matched analysis (PSM), two groups were compared: the PH group (patients submitted to resection for a first HCC) and the SH group (patients resected for intrahepatic rHCC after previous HCC-related treatments).

Results: 2689 patients were enrolled. PH included 2339 patients, SH 350. After PSM, 263 patients were selected in each group with major resected nodule median size, intraoperative blood loss and minimally invasive approach significantly lower in the SH group. Long-term outcomes were compared, with no difference in OS and DFS. Univariate and multivariate analyses revealed only microvascular invasion as an independent prognostic factor for OS.

Conclusion: SH proved to be equivalent to PH in terms of safety, feasibility and long-term outcomes, consistent with data gathered from East Asia. In the awaiting of reliable treatment-allocating algorithms for rHCC, SH appears to be a suitable alternative in patients fit for surgery, regardless of the previous therapeutic modality implemented.

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Correspondence
Maurizio Iaria, Department of General and Specialized Surgery, Division of General Surgery, Parma University Hospital, Italy, Via Linati, 6, 43121, Parma, Italy. E-mail: miaria@ao.pr.it

Introduction

Hepatocellular carcinoma (HCC) is among the most common malignant neoplasms worldwide. HCC recurrence (rHCC) represents a major issue, strongly affecting patient survival after treatment. The reported recurrence rates after resection or percutaneous treatments span between 50% and 80%.[1,2] The ideal approach after recurrence has not been established yet. To date, clear guidelines dealing with such scenario are lacking and therapy is oftentimes chosen according to center's experience.

Liver transplantation (LT) might be the best suited treatment for these patients. However, shortage of donors keeps representing a major shortcoming. Salvage hepatectomy (SH) may be an effective curative option but related studies are based on small sample sizes, whereas published experiences on rHCC surgical therapy are limited and their outcomes are, at times, dissimilar. In addition, published Western experiences on the topic are limited comparing with those coming from much larger East Asian studies.

Given such a gap, we did evaluate the Italian experience on SH through an observational retrospective multicenter cohort nation-based study, part of the whole Hepatocarcinoma Recurrence on the Liver Study (He.RC.O.Le.S.) Italian Registry.

A propensity score matched analysis (PSM) was conducted to elude heterogeneity and reduce bias. Perioperative and oncological outcomes of patients submitted to SH after intrahepatic recurrence were compared to a matched group of patients submitted to primary hepatectomy (PH).

Safety and efficacy of SH in the setting of intrahepatic rHCC were finally assessed in our large Western cohort.

Methods

Registry informations, patient's and data acquisition

This is a large retrospective study based on a national cohort of patients enrolled by the Hepatocarcinoma Recurrence on the Liver Study Group (He.RC.O.Le.S.) which is an open network of Italian hepato-biliary centers sharing data and promoting scientific research on HCC. He.RC.O.Le.S. Registry includes patients who underwent curative liver resection for HCC. The study protocol was registered at *ClinicalTrial.gov* (ID NCT04053231). The study followed the ethical guidelines of the 1975 Declaration of Helsinki, as revised in Brazil 2013. The Ethical Committee of the Coordinating Center (San Gerardo Hospital, Monza, Italy, "Monza e Brianza Ethical Committee") reviewed and approved the protocol on 21 December 2018.

The Registry database included 163 variables, all data were submitted by local researchers and anonymized prior to submission to the Coordinating Centre. Data collection was performed using an electronic database system in all centers. The submitted data were then checked centrally at San Gerardo Hospital. Once examined, the record was accepted into the dataset for analysis. Data were processed and disseminated in anonymous form. Data management was accomplished by the Bicocca Clinical Research Office (BiCRO), which actively participated and supported the Study Group. The subject has the right, at all times, to obtain confirmation of the existence or otherwise of such data, know their content and origin, check their accuracy and ask for data additions or updating or rectification.

We divided the nation-based cohort (latest update April 2020) into two groups: 1) the PH group, which encompassed patients submitted to liver resection for a first diagnosis of HCC without any previous HCC-related treatment and 2) the SH group, including those who underwent liver resection for intrahepatic rHCC after a previous HCC-related treatment.

No distinction was made between local or distant intrahepatic recurrence.

Clinicopathological data

The following data were collected for each patient: age, sex, Charlson Comorbidity Index (CCI), HCV and HBV infection, presence of cirrhosis and its severity (MELD score, Child–Pugh score, presence of portal hypertension), indocyanine green retention rate at 15 min (ICGR15), HCC characteristics (number, location and size) and alpha-fetoprotein serum level (αFP:ng/mL). Portal hypertension was defined by the presence of esophagogastric varices, ascites or splenomegaly and a platelet count <100,000/mm3. Severity of the disease was classified according to the BCLC staging system. Patients were classified as first diagnosis or intrahepatic rHCC, data concerning timing and previous treatments were collected. Former therapy encompassed liver resection, chemoembolization (TACE) and percutaneous treatments such as radiofrequency (RF) or microwave (MW) ablation.

Operative and perioperative outcomes

Operative data included number of resected nodules, localization, type of resection, surgical approach (minimally invasive *vs.* open), conversion, presence of portal thrombosis, length of surgery, intraoperative ablative therapies, blood loss, length of hospital stay. Liver resections were defined according to the "Brisbane 2000 Terminology of Liver Anatomy and Resections". Major hepatectomies were classified as resection of three or more liver segments. Perioperative outcomes included morbidities and mortality (up to 90 days after surgery). Type and severity of postoperative complications were defined according to the Clavien-Dindo classification and CCI. Major complications were defined as Clavien-Dindo grade $\geq$3. Post-hepatectomy liver failure (PHLF) was defined according to the 50-50 criteria. Postoperative liver ascites was defined as a daily ascitic fluid drainage exceeding 500 mL or the presence of ascites at US scan in case of no drains for three consecutive days.

Pathology and follow-up

Pathology of resected specimens took into consideration tumor size, number of nodules, grade of tumor differentiation, macroscopic and microscopic vasculobiliary invasion, resection margins and possible extrahepatic disease. Resection margins were considered positive if < 1 mm. The oncological follow-up schedule included every 3-month visits for the first 2 years followed by subsequent every 6-month visits.[3]

Recurrence (rHCC) was defined as a new-onset lesion with suggestive radiological features.

Oncological outcomes

Overall survival (OS) and disease-free survival (DFS) rates were calculated starting from the upfront liver resection in the PH group and the time of salvage liver surgery in the SH group.

Statistical analysis

The PSM was used to minimize potential differences and to compare the treatment effects by considering all covariates that may determine differences in the population of the two groups.[4,5]

Propensity scores were estimated using logistic regression and including in the model the following covariates: age, HCV antibody, CCI, BCLC stage, number of nodules at preoperative imaging, portal vein invasion and tumor grading.

A 1:1 "nearest neighbor" case–control match without replacement was applied,[6] meaning that each patient treated for a local rHCC was matched with 1 patient treated for a primary HCC. All variables were compared before and after PSM.

Quantitative variables were presented as mean. Categorical variables were presented as numbers and percentages. Comparison of quantitative variables was performed using a Mann–Whitney *U* test. Comparison of categorical variables was performed using Pearson's Chi-squared test or Fisher's exact test depending on numbers. DFS and OS were calculated using the Kaplan–Meier method and survival curves were compared by using the log-rank test. Cox proportional hazards model was used for multivariate logistic regression analysis for factors with a *p-value* <0.15 in the univariate analysis.

Data differences between groups were considered statistically significant at *p-value* <0.05.

Analyses were performed using the SPSS software (version 11; SPSS, Inc, Chicago, IL).

Results

A total of 2689 patients were enrolled in He.RC.O.Le.S. 1 from January 2007 to December 2018. The PH group included 2339 patients while the SH group 350. Previous HCC treatments before surgery in the SH group comprised hepatic resection in 173 cases (49.3%), TACE in 64 (18.2%), percutaneous ablation in 99 (28.2%) and combined treatments in 14 (4.0%).%). Complete data on DFS in the SH group were only available in 177 cases over 350 with a median overall DFS after the first treatment of 24 months (95% CI, 20.5–27.4) with DFS rates at 1, 3, and 5 years of 77.7%, 33.5% and 14.9% respectively. Stratified for previous treatments, median DFS were 32 months (95% CI, 24–39.9) for liver resection, 24 months (95% CI, 16.6–30.3) for percutaneous ablation and 10 months (95% CI, 3.8–16.1) for TACE ($p = 0.01$). Besides, both DFS and OS did not differ after SH in relation with the primary treatment modality (Table 1).

Concerning perioperative outcomes, the laparoscopic approach was much more frequently used in the SH group after percutaneous ablation (48.9% percutaneous ablation, 20.9% liver resection, 20.4% TACE; $p < 0.001$).

We also compared, before PSM, the PH cohort with the SH after liver resection only (SHro) group. Such subset analysis showed a statistical difference in terms of laparoscopic approach (PH 35.9% vs SHro 20.9%, $p < 0.001$) in favor of PH. In addition, in the SHro cohort more combined intraoperative ablations (RFA or Microwaves) were observed (SHro 9.6% vs PH 5.5%, $p < 0.044$).

As to long-term outcomes, the 5-year DFS rate was comparable in the two subsets (PH 40.8% ± 0.1% vs SHro 39.4% ± 0.4%, $p = 0.690$), whereas the 5-year OS rate seemed to

Table 1 DFS and OS after SH stratified for primary treatment: Liver Resection vs TACE vs Percutaneous ablation

	Univariate analysis (DFS)						
	Liver resection		TACE		Percutaneous ablation		P value
	n.	*5-years %*	*n.*	*5-years %*	*n.*	*5-years %*	
DFS	166	39.4 ± 4.9	58	28.5 ± 7.9	87	33.1 ± 6.7	0.598
	Univariate analysis (OS)						
	Liver resection		TACE		Percutaneous ablation		P value
	n.	*5-years %*	*n.*	*5-years %*	*n.*	*5-years %*	
OS	167	74.4 ± 4.7	58	75.0 ± 7	89	65.7 ± 7.5	0.448

Table 2 Patients characteristics (Correlation between Clinicopathological features before and after PSM)

	Before PSM			After PSM		
	PH n = 2339	SH n = 350	P value	PH n = 263	SH n = 263	P value
Age (median [range])	70 (16–95)	72 (32–88)	**<0.001**	73 (44–91)	73 (32–88)	0.654
Sex (%)						
Male	1786 (76.4)	269 (76.9)	0.053	209 (79.5)	199 (75.5)	0.347
Female	552 (23.6)	81 (23.1)		54 (20.5)	64 (24.3)	
HCV antibody (%)						
Negative	1199 (52.5)	157 (46.4)	**0.021**	120 (45.6)	115 (43.7)	0.726
Positive	1083 (47.5)	181 (53.6)		143 (54.4)	148 (56.3)	
Charlson Score (median [range])	6.35 (2–14)	6.73 (2–12)	**0.005**	7 (2–14)	7 (2–12)	0.87
HBV antigen (%)						
Negative	1849 (81.1)	274 (80.8)	0.478	215 (81.7)	210 (79.8)	0.658
Positive	431 (18.9)	65 (19.2)		48 (18.3)	53 (20.2)	
MELD Score (median [range])	7 (4–57)	7 (3–17)	0.717	7 (4–18)	7 (3–17)	0.529
Cirrhosis (%)						
No	863 (37.4)	120 (35.0)	0.21	79 (30.0)	78 (29.7)	1
Yes	1444 (62.6)	223 (65.0)		184 (70.0)	185 (70.3)	
Oesophageal varices (%)						
No	1582 (80.9)	231 (79.9)	0.371	168 (78.5)	167 (76.6)	0.674
Yes	373 (19.1)	58 (20.1)		46 (21.5)	51 (23.4)	
Splenomegaly (%)						
No	1740 (81.7)	256 (80.5)	0.336	199 (79.3)	197 (77.9)	0.745
Yes	391 (18.3)	62 (19.5)		52 (20.7)	56 (22.1)	
ICG R-15 (median [range])	14 (1.6–54)	14.5 (1.7–53)	0.394	10 (1.8–74)	13 (1.4–54)	0.19
AFP ng/mL (median [range])	28 (1–80036)	15 (1–22232)	0.024	98 (1–17676)	105 (1–9722)	0.929
Larger nodule size (cm)- CT-scan (median [range])	4 (0.3–21)	4 (1–20)	0.15	12 (1–105)	13 (2–147)	0.788
Larger nodule size (mm) - Pathology (median [range])	40 (1–280)	40 (1–220)	**<0.001**	40 (4–200)	30 (1–220)	**<0.001**
Number of nodules CT-Scan (%)						
Uninodular	1800 (79.6)	234 (70.1)	**<0.001**	201 (76.4)	190 (72.2)	0.318
Multinodular	461 (20.4)	100 (29.9)		62 (23.6)	73 (27.8)	
Number of nodules – Pathology (%)						
Uninodular	1849 (79.1)	240 (68.6)	**<0.001**	217 (83.1)	206 (78.6)	0.221
Multinodular	490 (20.9)	110 (31.4)		44 (16.9)	56 (21.4)	
Bilobar disease (%)						
Unilobar	1932 (89.6)	266 (86.1)	0.078	236 (91.8)	217 (86.8)	0.083
Bilobar	225 (10.4)	43 (13.9)		21 (8.2)	33 (13.2)	
Portal vein invasion (%)						
No	1895 (87.0)	273 (87.2)	1	229 (87.1)	229 (87.1)	1
Yes	282 (13.0)	77 (12.8)		34 (12.9)	34 (12.9)	
Microvascular invasion (%)						
No	1339 (65.2)	185 (60.5)	0.11	161 (62.9)	151 (59.9)	0.304
Yes	716 (34.8)	121 (39.5)		93 (36.3)	101 (40.1)	
BCLC Stage (%)						
0	214.0 (10.0)	55.0 (17.9)	**<0.001**	41.0 (0.1)	50.0 (0.1)	0.531
A	993.0 (46.5)	137.0 (44.5)		131.0 (0.4)	120.0 (0.4)	
B	571.0 (26.7)	69.0 (22.4)		56.0 (0.2)	53.0 (0.2)	

Table 2 (*continued*)

	Before PSM			After PSM		
	PH n = 2339	SH n = 350	P value	PH n = 263	SH n = 263	P value
C	357.0 (16.7)	45.0 (14.6)		35.0 (0.1)	38.0 (0.1)	
D	2.0 (0.1)	2.0 (0.6)		0	2.0 (0.008)	
Grading (%)						
G1	257 (11.6)	35 (11.1)	0.9	16 (6.1)	28 (10.6)	0.213
G2	1347 (60.5)	185 (58.9)		178 (67.7)	161 (61.2)	
G3	583 (26.2)	88 (28.0)		66 (25.1)	70 (26.6)	
G4	38 (1.7)	6 (1.9)		3 (1.1)	4 (1.5)	
Margin (%)						
R0	1841 (89.8)	235 (82.7)	0.002	228 (89.8)	208 (83.5)	0.089
R1	196 (9.6)	46 (16.2)		24 (9.4)	39 (15.7)	
R2	14 (0.7)	3 (1.1)		2 (0.8)	2 (0.8)	
Resection margin (median [range])	5 (0–120)	5 (0–65)	0.001	5 (0–35)	5 (0–65)	0.216
Extrahepatic disease (%)						
No	2090 (95.1)	301 (93.5)	0.132	252 (95.8)	243 (92.7)	0.137
Yes	107 (4.9)	21 (6.5)		11 (4.2)	19 (7.3)	
Satellitosis (%)						
No	1268 (78.7)	195 (79.6)	0.801	134 (77.9)	150 (80.2)	0.606
Yes	343 (21.3)	50 (20.4)		38 (22.1)	37 (19.8)	
Capsule (%)						
No	748 (55.5)	146 (67.0)	**0.002**	90 (60.8)	121 (68.4)	0.163
Yes	599 (44.5)	72 (33.0)		58 (39.2)	56 (31.6)	

be better in the SHro cohort (74.7% ± 4.7% vs 66.1% ± 1.4%, $p = 0.033$).

Median follow-up was 38.7 months (range: 1–151).

Patient's demographics and clinicopathological features, before and after PSM, are reported in Table 2. Before PSM, the two cohorts were different in terms of mean age, HCV infection, CCI, tumor size, presence of capsule, number of nodules and BCLC stage. Perioperative and pathological characteristics before and after PSM are reported in Table 3. After PSM the two groups differed in number of resected nodules, intraoperative ablation, type of resection and intraoperative blood loss.

Study population after PSM (preoperative features)

After PSM, two groups of 263 patients were selected. There were no significant differences in terms of gender, age and CCI indicating homogeneity of patient characteristics between the two groups. No differences were found in HCV and HBV infection rate ($p = 0.726$ and $p = 0.658$). Liver disease severity and liver function decline reflected by presence of cirrhosis, MELD score, Child-Pugh score, portal hypertension and ICGR15 were similar between PH and SH groups.

BCLC stage ($p = 0.531$), αFP serum level ($p = 0.929$), bilobar disease ($p = 0.083$), multinodularity ($p = 0.318$) as well as extrahepatic disease ($p = 0.137$), at the preoperative imaging, were all alike (Table 2).

Study population after PSM (intraoperative, postoperative and pathological features)

Despite the same amount of minor resections (77.6% in PH *vs.* 79.4% in SH; $p = 0.671$), an open approach was more commonly adopted in the SH group (69.5% *vs.* 58.6%; $p = 0.012$). No difference in conversion rate after laparoscopy was found ($p = 0.267$), same as for anatomical resection rate (60.8% in PH and 58.4% in SH; $p = 0.594$). Besides, near 60% of patients in both groups had uninodular resection ($p = 0.902$) with a comparable rate of synchronous intraoperative ablations ($p = 0.902$). In terms of radical resection rate, there was a tendency to perform more R1 resection in the SH cohort even in absence of statistical significance ($p = 0.089$). Intraoperative blood loss was significantly lower in the SH group, with a median of 265 mL (range 0–1600 mL) comparing to 350 mL (range 10–3500 mL) with a p-value 0.02. Overall postoperative complications, as per the Clavien-Dindo classification, and the CCI were similar ($p = 0.594$; $p = 0.813$), while major complications occurred in 17.9% of patients in the PH group and in 11.7% in the SH group, lacking statistical significance ($p = 0.132$). No differences were

Table 3 Perioperative outcomes (Correlation between perioperative outcomes features before and after PSM)

	Before PSM			After PSM		
	PH n = 2339	SH n = 350	P value	PH n = 263	SH n = 263	P value
Resection (%)						
Minor	1744 (78.0)	265 (81.0)	0.222	204 (77.6)	208 (79.4)	0.671
Major	493 (22.0)	62 (19.0)		59 (22.4)	54 (20.6)	
Surgical approach (%)						
Open	1321 (64.1)	203 (70.0)	0.057	150 (58.6)	173 (69.5)	**0.012**
Laparoscopy	739 (35.9)	87 (30.0)		106 (41.4)	76 (30.5)	
Conversion (%)						
No	618 (85.1)	74 (85.1)	0.545	94 (89.5)	63 (82.9)	0.267
Yes	108 (14.9)	13 (14.9)		11 (10.5)	13 (17.1)	
Type of resection (%)						
Anatomical	1470 (63.3)	192 (56.1)	**0.012**	160 (60.8)	153 (58.4)	0.594
Wedge	853 (36.7)	150 (43.9)		103 (39.2)	109 (41.6)	
Intraoperative Ablation (%)						
No	2158 (94.4)	303 (89.4)	**0.002**	238 (90.8)	238 (91.5)	0.902
RFA	108 (4.7)	31 (9.1)		18 (6.9)	18 (6.9)	
Mw	19 (0.8)	5 (1.5)		6 (2.3)	4 (1.5)	
Surgical time (minutes) (median [range])	250 (45–865)	250 (55–754)	0.391	240 (45–865)	240 (77–754)	0.659
Intraoperative blood loss (mL) (median [range])	300 (0–4000)	300 (0–1600)	**0.015**	350 (10–3500)	265 (0–1600)	**0.02**
Portal thrombosis (%)						
No	1865 (87.6)	276 (85.2)	0.0211	226 (86.9)	227 (87.0)	1
Yes	263 (12.4)	48 (14.8)		34 (13.1)	34 (13.0)	
Peroperative mortality (%)						
No	2312 (99.6)	346 (99.1)	0.2	261 (99.6)	259 (98.9)	0.624
Yes	9 (0.4)	3 (0.9)		1 (0.4)	3 (1.1)	
Hospital Stay (Day) (median [range])	8 (1–215)	7 (2–77)	0.063	8 (2–215)	7 (2–77)	0.285
Postoperative Complications (%)						
No	1437 (62.8)	217 (62.7)	1	154 (58.6)	160 (61.1)	0.594
Yes	853 (37.2)	129 (37.3)		109 (41.4)	102 (38.9)	
Postoperative Complications -Clavien>3 (median [range])						
No	1188 (84.5)	175 (89.3)	0.087	147 (82.1)	151 (88.3)	0.132
Yes	218 (15.5)	21 (10.7)		32 (17.9)	20 (11.7)	
Comprehensive Complication Index (CCI) (median [range])	20.9 (8–100)	20.9 (8–100)	0.878	20.9 (8–100)	20.9 (8–100)	0.813
Postoperative Liver Failure (%)						
No	2208 (95.1)	338 (97.1)	0.101	247 (94.3)	252 (96.6)	0.296
Yes	114 (4.9)	10 (2.9)		15 (5.7)	9 (3.4)	
90-day Mortality (%)						
No	2266 (97.5)	344 (98.9)	0.175	255 (97.3)	257 (98.5)	0.544
Yes	57 (2.5)	4 (1.1)		7 (2.7)	4 (1.5)	
Postoperative ascitis (%)						
No	2073 (89.4)	312 (89.7)	0.926	232 (88.5)	233 (89.3)	0.889
Yes	247 (10.6)	36 (10.3)		30 (11.5)	28 (10.7)	

Table 4 Univariate analysis of prognostic factors on DFS

	Univariate analysis (DFS)				
	PH		SH		P value
	n.	5-years %	n.	5-years %	
DFS	241	36.8 ± 4.0	241	37.0 ± 4.0	0.788
Age					
<75	139	38.6 ± 5.2	152	37.2 ± 5.1	0.739
≥75	102	33.7 ± 6.3	89	37.1 ± 6.7	
Sex					
Male	192	34.3 ± 4.7	183	40.5 ± 4.8	0.758
Female	49	42.7 ± 7.6	58	26.3 ± 7.2	
Child-Pugh grade					
A	176	37.5 ± 4.5	169	39.7 ± 4.7	0.61
B	11	77.1 ± 14.4	13	0.0 ± 0.0	
HBV antigen					
Negative	197	35.9 ± 4.4	191	36.3 ± 4.6	0.818
Positive	44	41.3 ± 9.4	50	40.1 ± 9.0	
HCV antibody					
Negative	110	35.7 ± 6.1	108	35.5 ± 5.9	0.751
Positive	131	37.8 ± 5.2	133	38.7 ± 5.5	
Cirrhosis					
Negative	70	34.5 ± 7.6	74	47.3 ± 7.2	0.839
Positive	171	37.9 ± 4.6	167	32.3 ± 4.8	
ICG R15 (%)					
< 10	19		23	12.4 ± 10.8	0.443
> 10	22	33.4 ± 11.7	35	36.4 ± 9.9	
Number of nodules. CT-scan					
1	183	39.2 ± 4.6	176	39.3 ± 4.6	0.748
>1	58	29.8 ± 7.7	65	29.9 ± 8.4	
Number of nodules. Resected					
1	145	36.6 ± 5.6	150	34.4 ± 4.8	0.676
>1	95	37.3 ± 5.7	89	42.7 ± 7.2	
Number of nodules. Pathology					
1	199	39.2 ± 4.4	191	39 ± 4.4	0.773
>1	41	26.6 ± 8.8	49	24.1 ± 11.6	
Nodule size. Pathology					
≤50 mm	169	39.2 ± 4.7	204	37.8 ± 4.5	0.907
>50 mm	71	30.0 ± 7.5	37	31.6 ± 9.6	
Grading sec. Edmonson					
G1	15	49.9 ± 13.6	27	45.2 ± 12.5	0.695
G2	162	39.2 ± 4.9	148	37.1 ± 5.3	
G3	62	24.2 ± 7.8	62	35.5 ± 7.2	
G4	2	/	4		
Oesophageal varices					
No	150	29.8 ± 5.6	153	33.1 ± 4.9	0.567
Yes	46	36.2 ± 8.1	47	27.4 ± 10.3	

(*continued on next column*)

Table 4 (*continued*)

	Univariate analysis (DFS)				
	PH		SH		P value
	n.	5-years %	n.	5-years %	
Splenomegaly					
No	182	36.8 ± 4.7	183	40.8 ± 4.5	0.602
Yes	51	34.0 ± 8.1	50	21.2 ± 9.8	
Microvascular invasion					
Negative	154	48.7 ± 4.9	141	40.6 ± 5.9	0.477
Positive	81	9.6 ± 5.8	89	31.7 ± 5.6	
Portal vein invasion					
Negative	209	35.5 ± 4.3	209	36.3 ± 4.4	0.843
Positive	32	46.0 ± 10.3	32	41.2 ± 10	
Disease extension					
Unilobar	216	39.9 ± 4.2	202	38.8 ± 4.4	0.674
Bilobar	19	/	27	13.5 ± 8.8	
BCLC					
0	37	33.6 ± 10.6	46	36.8 ± 9.1	
A	123	36.0 ± 5.5	108	32.1 ± 6.7	
B	49	42.7 ± 8.6	50	43.3 ± 8.1	
C	32	32.9 ± 10.1	35	40.5 ± 9.5	
Margins					
R0	219	36.6 ± 4.1	190	38.6 ± 4.6	0.808
R1	21	53.9 ± 13.3	36	21.1 ± 10.4	
Extrahepatic disease					
No	230	35.7 ± 4.1	222	35.6 ± 4.2	0.831
Yes	11	54.5 ± 15.0	18	50.4 ± 12.5	
Satellitosis					
No	118	31.8 ± 6.6	130	28.8 ± 5.8	0.832
Yes	33	7.8 ± 7.0	36	11.9 ± 6.9	
Capsule					
No	74	29.7 ± 7.7	105	27.4 ± 5.9	0.691
Yes	54	27.3 ± 10.7	53	27.6 ± 9.1	
Resection					
Minor	188	36.5 ± 4.4	193	37.8 ± 4.6	0.735
Major	53	37.8 ± 9.0	47	34.8 ± 9.1	
Technique					
Open	135	34.8 ± 5.3	156	35.0 ± 4.7	0.783
Laparoscopy	99	40.4 ± 6.1	72	39.6 ± 8.3	
If Laparoscopy. Conversion					
No	87	44.4 ± 6.5	60	50.1 ± 8.7	0.359
Yes	11	/	12		
Type of resection					
Anatomical	151	41.9 ± 5.0	142	43.6 ± 5.3	0.647
Wedge	90	27.1 ± 6.5	98	27.9 ± 6.0	
Intraoperative Ablation					

(*continued on next page*)

Table 4 (*continued*)

	Univariate analysis (DFS)				
	PH		SH		P value
	n.	5-years %	n.	5-years %	
No	220	38.0 ± 4.2	220	39.0 ± 4.3	0.977
RFA	14	19.5 ± 15.4	14		
Mw	6	60.0 ± 21.9	4	75.0 ± 21.7	
Intraoperative portal thrombosis					
No	207	35.9 ± 4.3	208	36.1 ± 4.4	0.861
Yes	32	45.9 ± 10.3	31	46.8 ± 10.8	
Postoperative Complications Clavien >3					
No	141	36.3 ± 4.9	145	40.4 ± 5.3	0.745
Yes	27	48.2 ± 11.3	17	32.3 ± 14.6	
Postoperative Liver Failure					
No	227	36.2 ± 4.1	233	37.3 ± 4.1	0.746
Yes	13	53.6 ± 18.8	7	25.0 ± 21.7	
Postoperative ascites					
No	213	37.8 ± 4.1	216	37.5 ± 4.3	0.763
Yes	27	17.1 ± 14.5	24	36.9 ± 12.7	

found in PHLF rate (PH 5.7% *vs.* SH 3.4%; $p = 0.296$) and post-operative ascites (PH 11.5% *vs.* SH 10.7%; $p = 0.889$). The median post-operative hospital stay was 8 days (range 2–215) in the PH group and 7 (range 2–77) in the SH group respectively ($p = 0.285$). The 90-day mortality rate was 2.7% in the PH group and 1.5% in the SH ($p = 0.544$) (Table 3).

Besides, pathology did not show any difference in terms of tumor grading, resection margins, microvascular invasion, portal vein invasion, satellitosis and presence of tumor capsule. Only the median size of the largest resected nodule was found to be significantly smaller in the SH group comparing to the PH group (median size 30 mm, range 1–220 *vs.* 40 mm, range 4–200; $p < 0.001$).

Long-term outcomes (OS, DFS) after PSM

Whole data on patient's survival were thoroughly collected in 241 out of 263 patients in each group. Median follow-up was 37.3 months (range 1–136). No differences in DFS were found between the two groups at 1,3 and 5 years after surgery (73.2%, 45%, 36.8% in PH *vs.* 75%, 47.9%, 37% in SH; $p = 0.788$).

The overall HCC recurrence rate summing both groups was 47.5% (250 patients) during the entire follow-up period.

Median OS was 86.7 months (95% CI, 78.3–95.1) in the PH and 101.7 (95% CI, 92.7–109.8) months in the SH group, with a log-rank test of 0.121.

The 1-, 3- and 5-year OS were 95.1%,71.4%, 60.8% in the PH group and 93.2%, 79.4% and 70.5% in the SH group ($p = 0.121$).

In the univariate analysis no variable considered (Table 4) was found to be a prognostic factor influencing DFS after surgical resection. Besides, with log-rank, none of them resulted in a p-value ≤ 0.15, therefore multivariate analysis was not conducted.

Concerning OS, only the absence of microvascular invasion (MVI) was found to be a favorable prognostic factor in the univariate analysis, with a 5-year survival rate of 82.8 ± 4.2% in the SH group versus 65.1 ± 5.3% in the PH group ($p = 0.027$). In the multivariate Cox's regression, each variable with a p-value ≤ 0.15 identified by univariate analysis was evaluated (age, gender, HBV and HCV infection, multinodularity, grading, splenomegaly, MVI, portal vein invasion, localization, resection margins, extrahepatic disease, major resection, surgical approach, type of resection, intraoperative ablation, post-operative major complications, PHLF and postoperative ascites). Only MVI proved to be an independent prognostic factor influencing OS (HR 2.11; 95% CI, 1.38–3.24; $p = 0.001$) (Table 5).

Discussion

Despite significant advances in diagnostic techniques and early effective treatments, rHCC is common and represents a major global health issue. After liver resection 5-year recurrence rate is about 50–70%, reaching up to 80% in patients treated with RFA.[1,2,7]

According to Tabrizian et al. recurrence also cause a 24% reduction in 5-year survival.[1] The existing treatment methods for rHCC mostly embrace salvage liver transplantation (SLT), SH, TACE, RFA, MW and percutaneous ethanol injection.[8] Physicians often feel confused about the best possible treatment in such setting and how to choose the most suitable strategy for each patient. Thus, the definitive therapeutic modality is often decided on the ground of clinician's experience or patient's preference. Hence, clear guidelines on rHCC treatment are lacking in the Western World[9] whereas the He.RC.O.Le.S group has recently completed the first nation-based Italian study, aiming to identify the best therapy among SH, thermoablation, TACE or Sorafenib by creating a machine-learning predictive model of survival after recurrence to allocate patients to their best potential treatment.[10] On the contrary, Japanese and Chinese guidelines recently attempted to address this issue recommending that rHCC should be treated similarly to the primary neoplasm.[11,12]

SH or SLT are still regarded as the ideal approach for rHCC. Though, questions have arisen regarding technical feasibility and safety of SH in patients who have already undergone percutaneous ablation, TACE or PH.

Actually, it would be reasonable to expect a higher perioperative risk comparing with PH in such population of patients.

Through an observational retrospective multicenter cohort nation-based study, part of the whole He.RC.O.Le.S. Italian Registry,[13] we sought to assess the safety and efficacy of SH for intrahepatic rHCC. Our data showed that SH can be safely performed with low morbidity and mortality rates. Both

Table 5 Univariate and multivariate analyses of prognostic factors on OS

Variable	*Univariate analysis (OS)*					*Multivariate analysis (DFS)*		
	PH		*SH*		*P value*	*HR*	*95% CI*	*P value*
	n.	*5-years %*	*n.*	*5-years %*				
OS	241	60.8 ± 4.3	244	70.5 ± 4.0	0.121	0.665	0.435–1.018	0.06
Age								
<75	139	61.2 ± 5.5	153	66.9 ± 5.2	0.123	1.03	0.68–1.559	0.89
≥75	102	60.9 ± 6.7	91	78.0 ± 6.0				
Sex								
Male	192	62.0 ± 4.8	184	70.6 ± 4.9	0.134	1.18	0.734–1.897	0.493
Female	49	57.4 ± 8.8	60	68.8 ± 7.5				
Child-Pugh grade								
A	176	57.5 ± 5.0	172	66.8 ± 5.3	0.267			
B	11	64.9 ± 16.7	13	54.5 ± 17.6				
HBV antigen								
Negative	197	62.4 ± 4.7	194	69.6 ± 4.6	0.121	1.426	0.772–2.635	0.257
Positive	44	55.7 ± 9.4	50	74.3 ± 8.1				
HCV antibody								
Negative	110	60.1 ± 6.5	108	68.6 ± 6.3	0.115	1.3	0.78–2.166	0.315
Positive	131	61.0 ± 5.7	136	72.7 ± 5.0				
Cirrhosis								
Negative	70	71.6 ± 7.2	74	84.1 ± 5.0	0.186			
Positive	171	57.2 ± 5.0	170	63.2 ± 5.5				
Number of nodules. Preop								
1	183	59.9 ± 4.9	178	73.4 ± 4.4	0.119			
>1	58	65.3 ± 7.9	66	61.7 ± 8.9				
Number of resected nodules								
1	146	53 ± 6.2	152	72.4 ± 4.7	0.108			
>1	94	69.2 ± 5.6	90	66.7 ± 7.4				
Number of nodules. Pathology								
1	199	58.7 ± 4.8	192	73.4 ± 4.2	0.115	0.621	0.333–1.156	0.133
>1	41	70.1 ± 8.1	51	55.7 ± 11.8				
Major nodule size. Pathology								
≤50 mm	170	64.7 ± 4.8	207	72.4 ± 4.4	0.324			
>50 mm	70	50.2 ± 9.1	37	58.9 ± 9.5				
Grading Edmonson								
G1	14	76.2 ± 12.1	27	63.2 ± 14.2	0.081	1.269	0.885–1.819	0.196
G2	162	66.8 ± 5.1	150	71 ± 5.3				
G3	63	41.9 ± 8.7	63	72.4 ± 6.9				
G4	2	/	4	66.7 ± 27.2				
Oesophageal varices								
No	150	54.7 ± 5.8	156	65.7 ± 5.4	0.256			
Yes	46	70.1 ± 9.5	47	70.5 ± 8.1				
Splenomegaly								
No	183	59.3 ± 5.0	185	74.1 ± 4.7	0.106	1.278	0.805–2.029	0.299
Yes	50	66.5 ± 8.6	51	61.3 ± 8.1				

(*continued on next page*)

Table 5 (*continued*)

Variable	*Univariate analysis (OS)*					*Multivariate analysis (DFS)*		
	PH		*SH*		*P value*	*HR*	*95% CI*	*P value*
	n.	*5-years %*	*n.*	*5-years %*				
Microvascular invasion								
Negative	154	65.1 ± 5.3	142	82.8 ± 4.2	**0.027**	2.119	1.384–3.244	**0.001**
Positive	81	48 ± 9.1	91	58.8 ± 7.0				
Portal vein invasion								
Negative	209	58.1 ± 4.7	212	70.9 ± 4.3	0.111	0.494	0.091–2.692	0.415
Positive	32	74.2 ± 8.4	32	76.2 ± 8.6				
Extension								
Unilobar	216	63.5 ± 4.3	205	73.6 ± 4.1	0.133	1.674	0.795–3.526	0.175
Bilobar	19	50.9 ± 15.8	27	32.8 ± 15.8				
BCLC								
0	37	45 ± 11.7	46	58.1 ± 11.4				
A	124	64.2 ± 5.9	110	78.1 ± 5.5				
B	48	54.2 ± 9.7	51	73.1 ± 7.3				
C	32	74.3 ± 8.5	35	62.3 ± 9.8				
Margin								
R0	211	60.7 ± 4.4	191	71.5 ± 4.4	0.104	1.324	0.782–2.243	0.296
R1	20	63.6 ± 13.8	38	55 ± 14.2				
Extrahepatic disease								
No	230	58.2 ± 4.5	225	72.7 ± 4.1	0.132	0.787	0.331–1.874	0.589
Yes	11	100±	18	42.6 ± 19.1				
Satellitosis								
No	119	55.2 ± 7.1	133	65.8 ± 6.1	0.306			
Yes	32	43.2 ± 13.1	36	54.4 ± 10.1				
Capsule								
No	75	58.5 ± 8.0	107	55.7 ± 6.7	0.36			
Yes	54	49.2 ± 11.1	54	82.0 ± 7.9				
Resection								
Minor	189	63.4 ± 4.8	196	71.0 ± 4.5	0.126	1.382	0.835–2.286	0.208
Major	52	61.1 ± 8.2	47	68.9 ± 8.8				
Technique								
Open	135	60.7 ± 5.4	159	66.9 ± 4.9	0.137	0.942	0.6–1.481	0.796
Laparoscopy	99	58.9 ± 7.1	72	79.1 ± 6.0				
If Laparoscopy. Conversion								
No	87	59.9 ± 7.5	60	86.6 ± 5.6	0.189			
Yes	11	62.5 ± 21.3	12	50.9 ± 15.8				
Type of resection								
Anatomical	150	66.3 ± 5.0	144	73.7 ± 5.1	0.094	1.538	0.969–2.442	0.068
Wedge	91	48.9 ± 8.0	99	65.9 ± 6.4				
Intraoperative Ablation								
No	220	60.8 ± 4.4	223	70.8 ± 4.1	0.143	0.741	0.362–1.518	0.412
RFA	14	51.9 ± 17.8	14	36.4 ± 27.2				
Mw	6	100.0	4	100.0				
Portal thrombosis Perop								

Table 5 (*continued*)

Variable	Univariate analysis (OS)					Multivariate analysis (DFS)		
	PH		SH		P value	HR	95% CI	P value
	n.	5-years %	n.	5-years %				
No	207	58.2 ± 4.8	211	70.4 ± 4.3	0.124	2.307	0.417–12.753	0.338
Yes	32	71.8 ± 8.5	31	70.4 ± 11.2				
Postoperative Complications Clavien >3								
No	141	64.8 ± 5.2	146	78.0 ± 4.6	0.181			
Yes	26	47.5 ± 16.1	17	54.5 ± 13.1				
Postoperative Liver Failure								
No	228	59.4 ± 4.4	236	71.4 ± 4.1	0.116	1.906	0.705–5.149	0.203
Yes	12	100.0	7	34.3 ± 19.5				
Ascites Postop								
No	213	63.7 ± 4.3	219	71.4 ± 4.2	0.149	1.077	0.566–2.053	0.821
Yes	27	55.4 ± 14.7	24	59.7 ± 13.0				

perioperative and oncological outcomes are comparable with tumor stage-matched patients who underwent PH for HCC. A laparoscopic approach was implemented more frequently in the PH group (41.4% *vs.* 30.5%; $p = 0.012$), which might be explained by major technical challenges provided by previous treatments. However, the Italian Group of Minimally Invasive Liver Surgery (IGoMILS) recently analyzed the national experience with the minimally invasive SH for rHCC, providing encouraging data over both its feasibility and safety.[14]

Torzilli et al. found that both operative time and intraoperative blood loss were significantly higher in patients who had already undergone percutaneous ablation before SH comparing with PH.[15] Interestingly enough, our data showed a lower intraoperative blood loss in the SH group comparing with PH (265 mL, range 0–1600 *vs.* 350 mL, range 10–3500; $p = 0.020$). No differences in terms of anatomical resections between the two groups (60.8% *vs.* 58.4%; $p = 0.594$) were observed. Still, we found a trivial trend towards more R1 resections (15.7% *vs.* 9.4; $p = 0.089$) in the SH group, explicable perhaps by additional technical and anatomical issues frequently encountered in the setting of salvage surgery.

In the resected specimens of our cohort, we found a significantly smaller median largest nodule size in the SH group comparing with the PH group (median size 30 mm, range 1–220 *vs.* 40 mm, range 4–200; $p < 0.001$), most likely due to early diagnosis of recurrence during closer routine follow-up after primary treatment. This was the solely mismatched perioperative feature documented after PSM population's selection.

The Clavien-Dindo grade ≥3 complication rate (11.7% *vs.* 17.9%, $p = 0.132$) and the 90-day mortality rate (1.5% *vs.* 2.7%; $p = 0.544$) were lower in the SH group, without statistical significance. Comparable outcomes were previously described after SH following non-surgical primary treatments, with a 90-day mortality rate ranging from 0 to 5% and a major complication rate between 6 and 28%.[16–18] A systematic review by Chan et al., including 22 studies, reported a mortality rate ranging from 0 to 6%, with a major complication rate between 0 and 32% after SH for intrahepatic rHCC.[19] Our nation-based data, collected from the largest Western series on SH to the best of our knowledge, seem to match those published from Eastern experiences in terms of safety. In addition, morbidity and mortality rates resemble those of PH.

The biological behaviour of rHCC after loco-regional treatments has been a matter of debate. Few authors emphasised its worse prognosis compared with primary HCC. In particular, according to Ruzzenente and Yoshida, ablative therapies such as RFA, might raise intra-tumoral pressure and hasten epithelial mesenchymal transition, promoting intravascular tumor spread.[20,21] Also, the amount of HCC complete necrosis after TACE appears to be quite low, near 10–20%[22] and the risk of intrahepatic recurrence or distant metastases from residual malignant cells could increase.[23] Yamashita et al. reported worse DFS and OS in SH carried out after RFA compared with SH for rHCC after PH. The authors speculate that a more aggressive pattern of recurrence after ablation, with features of microscopic and macroscopic portal venous tumor thrombi and a transition to poor differentiation, may have been affecting their outcomes.[24]

Despite the limit of some lacking information on the timing of previous treatments (177/350 cases), we analyzed the DFS in the SH group before rescue surgery (before PSM).

Patients who underwent TACE as first treatment had significantly shorter DFS (19.3 months; 95% CI, 9.7–29) than those treated with PH (37.3 months; 95% CI, 31.8–42.7) or percutaneous ablation like RFA and MW (33.8 months; 95% CI, 23.9–43.7).

In contrast, DFS and OS after SH (considering SH as time zero) were equivalent in our cohort once stratified for previous treatments (Table 1). Thus, the primary therapeutic modality carried out to treat HCC seemed to affect only "recurrence time", without influencing OS. Hence, liver resection should be firstly considered, when feasible, as salvage treatment for rHCC, no matter which approach has been implemented to treat the

primary neoplasm. Still, there is no clear consensus over the ideal modality to treat intrahepatic rHCC.[25,26]

Thus far, limited published series, mostly from East Asia, have been evaluating the long-term oncological outcomes after SH, leading to conflicting results (Table 6).

Sugo et al. did not find any difference in terms of short- and long-term outcomes after SH versus PH, whereas Yamashita et al. reported unsatisfactory long-term results in patients who underwent SH for rHCC.[17,24]

Still, when comparing such series, the 5-year OS does not seem to be dissimilar or affected by the nature of primary treatment.

Percutaneous treatments for rHCC are very often implemented and largely described in literature. Ueno et al. reported that multiple previous RFA before a SH were correlated with poor prognosis.[16] In a recent meta-analysis, Gavrilidis et al. did not find any significant difference in both 5-year DFS (HR 0.86; 95% CI, 0.67–1.11, $p = 0.250$) and 5-year OS (HR 1.03; 95% CI, 0.83–1.27, $p = 0.082$) in patients who underwent SH or RFA for rHCC.[36]

Surprisingly, TACE appeared to be better in terms of both OS and DFS comparing with SH or RFA according to Jin et al. in the subgroup of patients with MVI ($p = 0.03$ and $p = 0.05$, respectively).

TACE was particularly effective in improving OS in case of early rHCC associated with MVI when compared to SH or RFA ($p = 0.01$).[37]

Chan et al. reported a significantly poorer 5-year survival rate, after MELD score adjustment, when RFA was compared to SH or SLT (11.4%, 48%, 50% respectively; $p < 0.003$).[19]

From a speculative standpoint, SH should represent the ideal therapeutic option for rHCC, apart from SLT. With SH the surgeon is more capable to achieve free-margins and to eradicate those rHCCs associated with intrahepatic vascular invasion, thanks to anatomical resections.

In addition, SH helps to assess "hands on" the real extent of the recurrence, which is often unclear at the preoperative imaging, due to previous percutaneous ablative treatments and/or TACE.

Table 6 Comparison between SH series for long-term outcomes (DFS, OS)

				DFS			OS		
AUTHOR year	N°	Percutaneous treatment	Surgery	1 year (%)	3 year (%)	5 year (%)	1 year (%)	3 year (%)	5 year (%)
Yamashita Y 2015 (24)	46	46			34	17		58	52
Hu RH 1996 (27)	50	50		48	27	13	69	52	44
Sugo H 2012 (17)	23	23		65	41	33	91	91	67
Kishi Y 2017 (18)	62	62		58	36	22	90	79	67
Orimo T 2018 (28)	90	90		81	58	54			47
Fang JZ 2020 (29)	78		78	64	37	37	92	60	55
Chok KS 2012 (30)	47		47	44	27	0	81	55	44
Wu CC 2009 (31)	149		149			44			52
ItamotoT 2007 (32)	84		84	56	25	10	88	67	50
Minagawa M 2003 (33)	67		67	50	21	17	93	70	56
Song KD 2015 (34)	39		39	66	49	43	98	85	72
Eisele RM 2013 (35)	27	2	25	82	45	28	100	68	39
He.RC.O.Le.S 2021	314	147	167			37			70

*highlighted in yellow published series of SH after percutaneous treatments.
References: [17,18,24,27–35].

Such advantages are also pointed out by our large national cohort study. We did not find any statistically significant difference in terms of anatomical resection rate between PH and SH, although with a slight trend towards more R1 resections in the SH group (9.4% *vs.* 15.7%, $p = 0.089$). A recent systematic review and Bayesian network meta-analysis by Zheng et al. compared the efficacy and prognosis, in terms of oncological outcomes, of different strategies for intrahepatic rHCC. A total of 5 therapeutic interventions were assessed over 21 studies, involving 2818 patients. SLT and SH were the top two treatments in terms of OS and DFS, either for small HCC ($\leq$3 cm) or large HCC (>3 cm).[38]

Still, as highlighted by Kishi et al., SH is not always feasible and it can be offered as therapeutic option in no more than half of the patients affected by rHCC (6–53%).[18]

In conclusion, our study carries some limitations, it is merely retrospective and treatments other than SH were not considered for comparison, potentially leading to selection bias.

Still, as far as we know, this is the largest Western series about SH for rHCC, which provides significant data about its safety and feasibility.

The He.RC.O.Le.S. Italian Registry analysis confirmed equivalent perioperative outcomes between SH and PH, resembling data already published by East Asia groups.

Besides, SH led to favorable long-term oncological outcomes, especially 5-year OS, in such group of rHCC selected patients.

In the awaiting of reliable treatment-allocating algorithms for rHCC, SH should always be considered as a valid option and probably be preferred in patients fit for surgery, regardless of the previous therapeutic modality.

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Conflicts of interest

None declared.

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