Research article

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Minimally invasive hepatectomy *vs.* thermoablation for single small (≤3 cm) hepatocellular carcinoma: A weighted real-life national comparison

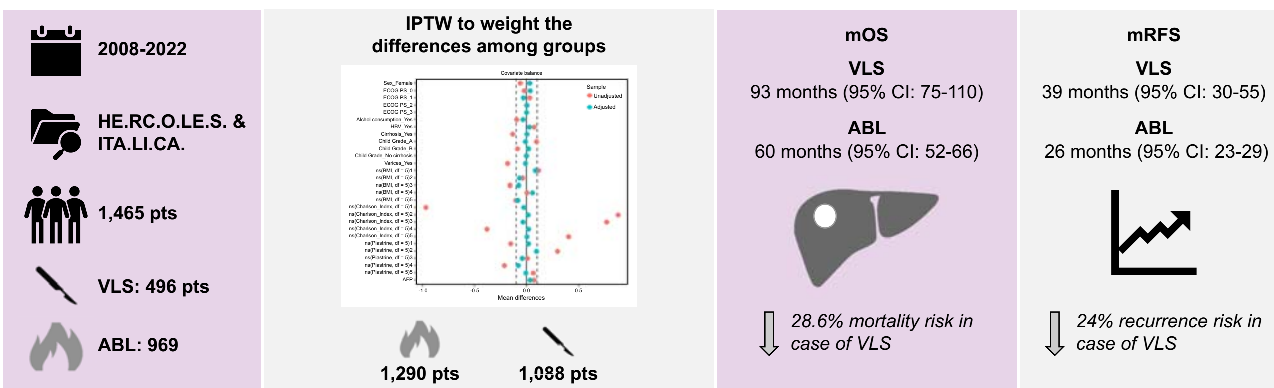
Authors

Felice Giuliante, Simone Famularo, Sara Grasselli, ..., Davide Bernasconi, Francesco Ardito, Franco Trevisani

Correspondence

felice.giuliante@policlinicogemelli.it (F. Giuliante).

Graphical abstract



Highlights:

- Real-world data analysis based on two national registers.
- Laparoscopic liver resection ensured prolonged overall and recurrence-free survival compared with ablation.
- Laparoscopic liver resection significantly reduced the risk of early recurrence after treatment.
- These trends were confirmed even in subgroup analysis and after weighting all the possible differences among groups.

Impact and implications:

Percutaneous thermoablation is considered an appropriate alternative to liver resection for small (≤3 cm) single hepatocellular carcinoma because of not-inferior overall survival, although several authors reported increased recurrence risk. Whether videolaparoscopic liver resection could guarantee comparable survival but superior oncologic control of the disease is a matter of debate. This study comparing videolaparoscopy *vs.* thermoablation in a large national cohort of 1,465 patients observed that the former guaranteed significant prolonged OS (93 months [95% CI 75–110] *vs.* 60 months [95% CI 52–66] for the ablation group) and recurrence-free survival (26 months [95% CI 23–29] for ablation patients and 39 months [95% CI 30–55] for laparoscopic resection patients) even after weighting all the preoperative and oncologic differences among the groups. Our results clearly address the need to rethink the role of thermoablation for single small HCC as a second-line treatment when laparoscopic liver resection is not feasible.

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Minimally invasive hepatectomy *vs.* thermoablation for single small (≤3 cm) hepatocellular carcinoma: A weighted real-life national comparison

Felice Giuliante[1,*,†], **Simone Famularo**[1,2,†], Sara Grasselli[3], Angelo Sangiovanni[4], Alessandro Vitale[5], Giuseppe Cabibbo[6], Andrea Lauterio[7], Federica Cipriani[8], Alice Saccomandi[9], Marco Arru[10], Elisa Pinto[11], Maurizia Rossana Brunetto[12], Maria Stella Franzè[13], Camilla Graziosi[14], Claudia Campani[15], Fabio Marra[15], Mariella Di Marco[16], Mariarosaria Marseglia[17], Valentina Santi[18], Mario Capasso[19], Alberto Masotto[20], Andrea Fontana[21], Maurizio Iaria[22], Alba Rocco[23], Matteo Serenari[24], Andrea Mega[25], Antonio Gasbarrini[26], Maria Corina Plaz Torres[27,28], Mattia Garancini[29], Simone Conci[30], Elton Dajti[31], Pasquale Perri[32], Rodolfo Sacco[33], Mariano Giglio[34], Cecilia Ferari[35], Michela De Angelis[36], Albert Troci[37], Donatella Magalotti[38], Daniele Nicolini[39], Giuseppe Zimmitti[40], Paola Germani[41], Laura Schiadà[42], Maria Conticchio[43], Matteo Zanello[44], Maurizio Romano[45], Flavio Milana[46], Quirino Lai[47], Stefan Patauner[48], Antonio Frena[48], Massimo Rossi[47], Guido Torzilli[46], Giacomo Zanus[45], Elio Jovine[24], Riccardo Memeo[43], Gianluca Svegliati-Baroni[42], Paola Tarchi[41], Moh'd Abu Hilal[40], Marco Vivarelli[39], Michele Crespi[37], Luigi Boccia[36], Guido Griseri[35], Roberto Ivan Troisi[34], Gian Luca Grazi[49], Francesco Azzaroli[31], Andrea Ruzzenente[30], Fabrizio Romano[29], Edoardo G. Giannini[27,28], Matteo Cescon[24], Gerardo Nardone[23], Raffaele Dalla Valle[22], Alessandro Ferrero[21], Filomena Morisco[19], Fabio Piscaglia[17], Giorgia Ghittoni[14], Carlo Saitta[13], Filippo Pelizzaro[11], Gianpaolo Vidili[10], Francesco Giuseppe Foschi[9], Luca Aldrighetti[8], Luciano De Carlis[7], Umberto Cillo[5], Elisabetta Biasini[3], Davide Bernasconi[50], Francesco Ardito[1,‡], Franco Trevisani[18,‡], for the HE.RC.O.LE.S. and the ITA.LI.CA. groups[§]

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Background & Aims: For patients with single small (≤3 cm) hepatocellular carcinoma ablation is the first-line treatment, although a high rate of recurrence has been reported. The aim was to compare videolaparoscopic liver resection (laparoscopic resection group) *vs.* percutaneous thermoablation (ablation group) in terms of overall survival, recurrence-free survival and early recurrence in a real-life national scenario.

Methods: The study is a retrospective collection with subsequent survival analysis. Data were collected from two Italian HCC registries, ITA.LI.CA and HE.RC.O.LE.S. An inverse probability of treatment weighting analysis was performed to balance baseline differences between groups. The Kaplan–Meier method and double-robust Cox multivariable regression were run to estimate the survival and the risk of mortality and recurrence.

Results: Between 2008 and 2022, 1,465 patients were enrolled. The laparoscopic resection group and ablation group consisted of 496 and 969 patients, respectively. At baseline, the ablation group had more advanced liver disease, with higher rates of cirrhosis (90.7% *vs.* 77.3%, p <0.001) and Child-Pugh B status (18.4% *vs.* 8.8%, p <0.001). After a median follow-up of 59 months and after weighting median overall survival was 60 months (95% CI 52–66) for the ablation group and 93 months (95% CI 75–110) for the laparoscopic resection group (hazard ratio [HR] 0.607, 95% CI 0.533–0.691, p <0.001). Median recurrence-free survival was 26 months (95% CI 23–29) for the ablation group and 39 months (95% CI 30–55) for the laparoscopic resection group (HR 0.736, 95% CI 0.659–0.822, p = 0.0013). Laparoscopy was associated with a reduced risk of early recurrence (HR 0.747, 95% CI 0.655–0.853, p = 0.011).

Conclusions: This study provides real-world evidence that for patients with single ≤3 cm HCC, videolaparoscopic liver resection offers superior long-term oncological outcomes compared with thermoablation. These findings support the preference for surgical treatment in this patient population.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and represents the fifth leading cause of cancer-related deaths worldwide.[1] Despite advancements in viral hepatitis prevention and antiviral therapies, its incidence is projected to rise, particularly in Western countries, as a result of

* Corresponding author. Address: Hepatobiliary and General Surgery Unit, Foundation University Hospital "A. Gemelli" IRCCS, Sacred Heart Catholic University, Viale Agostino Gemelli 8, 00136 Rome, Italy.
E-mail address: felice.giuliante@policlinicogemelli.it (F. Giuliante).

† These authors share co-first authorship.

‡ These authors share co-last authorship.

§ For the list of HE.RC.O.LE.S and ITA.LI.CA contributors please see Appendix 1.

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the increasing prevalence of metabolic-associated liver disease.[2] Currently, liver transplantation is considered the gold standard treatment, especially for HCC arising in the context of chronic liver disease.[3] However, because of organ shortages, thermoablation and liver resection remain viable curative-intent options, particularly for patients with preserved liver function.[4]

In cases of early-detected small single HCCs, numerous observational studies and randomized clinical trials (RCTs) have sought to compare the outcomes of surgery and ablation to determine the most effective personalized management for these patients.[5] Although some studies reported comparable outcomes in terms of survival and recurrence rates, others yielded conflicting results favoring one technique over the other.[6–10] Nonetheless, these studies varied significantly in their definitions of 'small HCC' and, in some cases, did not specifically focus on this subset of patients. Consequently, meta-analyses based on these studies have produced controversial conclusions.[11–13]

In response, clinical practice guidelines from both Western and Eastern societies recommend either surgical resection or ablation for HCC presenting as a single nodule <3 cm, with ablation being the preferred approach for nodules ≤2 cm in size or those located in deep areas.[14–16]

One of the primary advantages of ablation over surgery is its minimally invasive nature, alongside superior cost-effectiveness and suitability for treating frail patients who are otherwise ineligible for surgery.[17,18] However, the adoption of minimally invasive surgical techniques and advancements in perioperative management[19,20] have significantly narrowed the gap between surgery and percutaneous ablative procedures in terms of invasiveness and postoperative care. As a result, comparing the medium-to long-term outcomes of these two treatments has become increasingly critical to guide therapeutic decision-making.

To provide additional insights into this highly nuanced context, the present study compared the outcomes of minimally invasive surgery and percutaneous thermoablation in a real-life national setting for patients with single small (≤3 cm) HCC.

Patients and methods

Registers information

This retrospective study evaluated data prospectively collected by two Italian databases on HCC, the ITA.LI.CA (Italian Liver Cancer) and the HE.RC.O.LE.S. (Hepatocarcinoma Recurrence on the Liver Study). The ITA.LI.CA patients were enrolled between 1996 and 2022 by 24 different centers, whereas the HE.RC.O.LE.S. cases were enrolled between 2008 and 2022 by 30 centers.[21] More details are available in Supplementary methods 1.

Study overview, patient selection, and study design

All consecutive adult (age ≥18 years) patients with a radiological and/or histological proven HCC who underwent minimally invasive (videolaparoscopic) liver resection or percutaneous thermoablation from January 2008 to December 2022 were considered for this study. Results are reported according to principles of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[22] A checklist is available within the supplementary materials. The laparoscopic resection group cohort was extracted by the HE.R-C.O.LE.S. database, and the patients who underwent ablation were selected from the ITA.LI.CA database. The first register is a national database where patients treated by liver resection only (open or minimally invasive) are included. The latter is a hepatologic register where all the other treatments are collected but not liver resection.

Inclusion criteria were: (1) patients assigned to videolaparoscopic liver resection or percutaneous thermoablation as first HCC treatment without previous therapies; (2) evidence of single intrahepatic nodule with major diameter ≤3 cm. Exclusion criteria were: (1) extrahepatic tumor spread; (2) presence of macrovascular invasion; (3) missing data on the follow-up.

Selected patients were then divided into those who were treated by videolaparoscopic surgery (laparoscopic resection group) and those who underwent thermoablation (ablation group).

Causal question

What is the effect of laparoscopic surgery compared with percutaneous thermal ablation on overall survival in patients with a single HCC measuring ≤3 cm?

Study endpoints and follow-up

The primary endpoint was the overall survival (OS) across the two groups, measured as the difference in months between the date of treatment and that of death or the last follow-up available. The secondary endpoint was the recurrence-free survival (RFS), measured as the difference in months between the date of treatment and the date of the disease recurrence. In case of no recurrence, progression, or death, data were censored at the date of the last available follow-up visit. A recurrence before 24 months from the treatment was defined as 'early recurrence', and considered a surrogate of treatment strategy failure.

All patients were followed up using local protocols, which included measurement of serum alpha-fetoprotein (AFP), abdominal ultrasound, computed tomography (CT) scan or magnetic resonance imaging (MRI), and outpatient visits. Patient surveillance was closed at the end of December 2023.

Treatments

The indication for liver resection or thermoablation was provided by the multi-disciplinary board of each center including surgeons, hepatologists, oncologists, radiologists, interventional radiologists, and pathologists. The board decision was based on several factors, such as liver function, tumor burden (size and number of lesions, uni/bilobar disease, residual liver volume after resection, localization of the nodule), comorbidities, previous surgical history, patient's opinion, and level of available scientific evidence to provide a patient-tailored treatment in line with the precision medicine approach and according to a personalized management of HCC patients. The laparoscopic technique was decided by the surgical team, according to their expertise and general behavior. The ablation group included both patients undergoing percutaneous radiofrequency ablation (RFA) or microwave ablation (MWA). Compared with RFA, the larger volume of active heating of

MWA offers the possibility to treat a larger area, at higher temperature with a less susceptibility to the heat-sink effect of blood flowing. The choice of one or another technique was made according to clinical scenario and local expertise.

Definitions

Comorbidities were summarized by the Charlson Comorbidity Index (CCI).[23] Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) was measured at the first outpatient visit.[24,25] The presence of cirrhosis was established before the treatment choice according to clinical, biochemical, endoscopic, and, if available, pathological information. The presence of esophagogastric varices was assessed endoscopically. Liver function was estimated using both the model for end-stage liver disease (MELD) score[26] and the Child–Pugh–Turcotte (CPT) class.[27] Biochemical variables were obtained within 2 weeks from the assigned treatment. The number and size of nodules and presence of vascular invasion were assessed by CT scan or MRI, and each center declared that images were scrutinized by expert and dedicated radiologists. The extension of liver resection was defined as minor or major, based on the Brisbane nomenclature.[28]

Statistical analysis

The sample description was done using median and IQR for numeric variables and number and proportion for categorical variables. Mann–Whitney and Fisher tests were used to compare baseline patient characteristics between the two treatment groups. The issue of unmeasured values in some covariates (caused by a 'missing at random' [MAR] mechanism[29]) was handled by using the multiple imputation method, and final estimates of the coefficients and standard errors were obtained by pooling model results on 10 imputed datasets.[30] After the univariate comparison of baseline characteristics between treatment groups, all variables showing a p value <0.05 and with a known prognostic role were considered as confounders and included in a multiple logistic regression model. The model was fitted to each of the 10 datasets to estimate the propensity score (PS) (in our model: sex, ECOG-PS, alcohol consumption, cirrhosis, CPT class, presence of varices, BMI, CCI, platelet count, and AFP). For each patient, the estimated PS was used to run an inverse probability of treatment weighting (IPTW) analysis[31,32] (target estimand: average treatment effect). For continuous variables, splines with a df = 5 were applied. The generated weights over the 99th percentile were trimmed to stabilize the effect. After weighting each patient, two pseudo-populations of size different from the original ones but with comparable baseline characteristics were obtained. Standardized mean differences of confounders were calculated in both the original and weighted populations to check the balance between treatment groups, and a 'Love' plot (that graphically displays the pre and post effects of propensity scores) was generated. Survival was estimated by the Kaplan–Meier method, and comparisons were performed by the log-rank test before the IPTW and with a robust test after IPTW. A univariate Cox regression analysis was used to evaluate the prognostic role of baseline variables. Variables that were associated with OS by a p value <0.05 were included in the multivariable model, together with other well-known factors related to mortality. These data were reported as hazard ratio (HR) and 95% CI. The same analysis was performed for RFS. As a sensitivity analysis, a 1:1 nearest neighbor propensity score matching (target estimand: average treatment effect in the treated group) was run with a caliper of 0.1 with the same variables used for the IPTW.

The risk analysis for mortality and recurrence according to the treatment received was done also in different subgroups, after re-estimating the PS and the weights. The superiority of the laparoscopic resection over ablation was assessed in case a 5% significance level was achieved. Non-inferiority of laparoscopic resection over ablation was assessed by establishing the upper bound of the confidence interval for the difference in treatment effects (hazard ratio) that falls below a predefined margin (1.2). This value was chosen by clinical relevance according to the authors' opinion. Because of the retrospective nature of the study, this last measurement should be considered an exploratory analysis, and for that the hypothesis test and the consequent p value was not reported to avoid any unpowered analysis.

All the analyses were computed by using the open-source R software (v. 4.2.2, specific packages used: MICE, WeightThem, Cobalt, Survival, Survminer).

Results

Between 2008 and 2022, 13,608 patients (8,166 in the ITA.L-I.CA. register and 5,442 in the HE.RC.O.LE.S. register) were enrolled. Of these, 1,465 were included according to the inclusion and exclusion criteria: 496 were treated by laparoscopic hepatic resection (laparoscopic resection group) and 969 by percutaneous thermoablation (ablation group). A flow chart is available in Fig. S1.

At the baseline, 304 (31.4%) patients in the ablation group and 124 (25.0%) in the laparoscopic resection group were female (p = 0.013). Median age was 70 (IQR 62–76) years and 69 (IQR 61–75) years for the ablation and laparoscopic resection groups, respectively (p = 0.138). Median CCI score was 7 (IQR 6–9) and 6 (IQR 4–7), respectively (p <0.001). Alcohol consumption was the etiology of the underlying liver disease in 290 (31.9%) patients and 107 (21.9%) in the ablation and laparoscopic resection group, respectively (p <0.001). Cirrhosis was detected among 863 (90.7%) patients in the ablation group and 382 (77.3%) in the laparoscopic resection group (<0.001), and 162 (18.4%) patients and 36 (8.8%) patients were CPT grade B respectively (p <0.001). Esophagogastric varices were present in 433 (50.1%) and 139 (31.2%) patients in the ablation and laparoscopic resection groups (p <0.001). Regarding the tumor burden, median size was 2.00 cm (IQR 1.50–2.50) for ablation and 2.00 cm (IQR 1.50–2.40) for laparoscopic resection groups (p = 0.965); median AFP was 7.00 ng/dl (IQR 3.60–21.00) and 8.00 ng/dl (IQR 3.80–43.00) for ablation and laparoscopic resection groups, respectively (p = 0.042). These and other baseline characteristics are reported in Table 1. The rate of missing data in the whole dataset is reported in Table S1. Among the laparoscopic resection cohort, 334 (67.3%) patients underwent non-anatomic resection, and 162 (32.7%) underwent anatomic resection.

Over a median follow-up of 59 months (IQR 30–93), 637 (43.5%) patients died, and 792 (54.1%) had a recurrence. Median OS was 61 months (95% CI 56–66) for patients who underwent ablation and 90 months (95% CI 75–107) for those

Table 1. Baseline characteristics of the observed cohort.

	Ablation	Laparoscopic resection	*p* value
n	969	496	
Age (median [IQR])	70.00 [62.00-76.00]	69.00 [61.00-75.00]	0.138
Females (%)	304 (31.4)	124 (25.0)	0.016
Charlson Comorbidity Index (median [IQR])	7.00 [6.00-9.00]	6.00 [4.00-7.00]	<0.001
ECOG PS (%)			0.001
0	850 (87.7)	421 (84.8)	
1	97 (10.0)	65 (13.2)	
2	22 (2.3)	10 (2.0)	
Alcohol consumption (%)	290 (31.9)	107 (21.9)	<0.001
HBV+ (%)	93 (11.1)	87 (17.9)	0.001
HCV+ (%)	568 (63.5)	295 (59.8)	0.193
Cirrhosis (%)	863 (90.7)	382 (77.3)	<0.001
Child–Pugh grade (%)			<0.001
A	714 (81.1)	374 (91.2)	
B	162 (18.4)	36 (8.8)	
C	4 (0.5)	0 (0.0)	
Varices (%)	433 (50.1)	139 (31.2)	<0.001
MELD score (median [IQR])	8.03 [7.00-10.00]	8.00 [7.00-10.00]	0.358
Size, cm (median [IQR])	2.00 [1.50-2.50]	2.00 [1.50-2.40]	0.965
AFP, mg/dl (median [IQR])	7.00 [3.60-21.00]	8.00 [3.80-43.00]	0.042
Albumin, g/dl (median [IQR])	3.80 [3.50-4.10]	3.90 [3.50-4.30]	0.065
INR (median [IQR])	1.12 [1.04-1.20]	1.10 [1.04-1.22]	0.706
Platelet count × 10^9/L (median [IQR])	122.00 [84.00-165.00]	142.00 [92.00-187.00]	<0.001
MVI+ (%)	–	136 (27.4)	–
Satellitosis (%)	–	44 (8.8)	–
Anatomic resection (%)	–	179 (36.1)	

Continuous variables were compared using the Mann–Whitney test and categorical variables were compared with the Fisher test. AFP, alpha-fetoprotein; ECOG PS Eastern Cooperative Oncologic Group - Performance Status; MELD, model for end-stage liver disease; MVI, microvascular invasion at the histologic specimen; VLS, videolaparoscopy.

who underwent laparoscopic resection (*p* <0.001). Median RFS was 25 months (95% CI 23–29) for the ablation group and 38 months (95% CI 30–55) for the laparoscopic resection group (*p* <0.001). The survival curves are depicted in Fig. 1A and B.

Survival analysis after IPTW

The IPTW model adopted to balance the baseline differences between groups included: sex, ECOG-PS, alcohol consumption, cirrhosis, CPT class, presence of varices, BMI, CCI, platelet count, and AFP. The effect of the IPTW is depicted in Fig. 2, and the standard mean differences before and after the weighting are reported in Table S2. The weights distribution by treatment arm is depicted in Fig. S2: the overlapping of the weights' range allowed confirmation of the positivity assumption. After the weighting, two generated pseudo-populations consisted of 1,290.176 pseudo-patients in the ablation group and 1,088.217 pseudo-patients in the laparoscopic resection group.

In the weighted cohort, median OS was 60 months (95% CI 52–66) for the ablation group and 93 months (95% CI 75–110) for the laparoscopic resection group (HR 0.607, 95% CI 0.533–0.691, *p* <0.001) (Fig. 1C). At the multivariable double robust Cox regression, being treated by laparoscopic resection (HR 0.714, 95% CI 0.57–0.89, *p* = 0.003), ECOG-PS 2 (HR 2.108, 95% CI 1.30–3.40, *p* = 0.002), being Child–Pugh B (HR 1.729, 95% CI 1.28–2.33, *p* <0.001), age (HR 1.012, 95% CI 1.00–1.02, *p* = 0.017) and an early recurrence after treatment (HR 1.781, 95% CI 1.46–2.16, *p* <0.001) were independently associated with the OS (Table 2). The effect of the treatment was tested also in different subgroups (exploratory analysis), and the results were depicted in Fig. 3A. Briefly, in case of tumors ≤2 cm, laparoscopic resection (HR 0.656, 95% CI 0.48–0.89) was associated with OS.

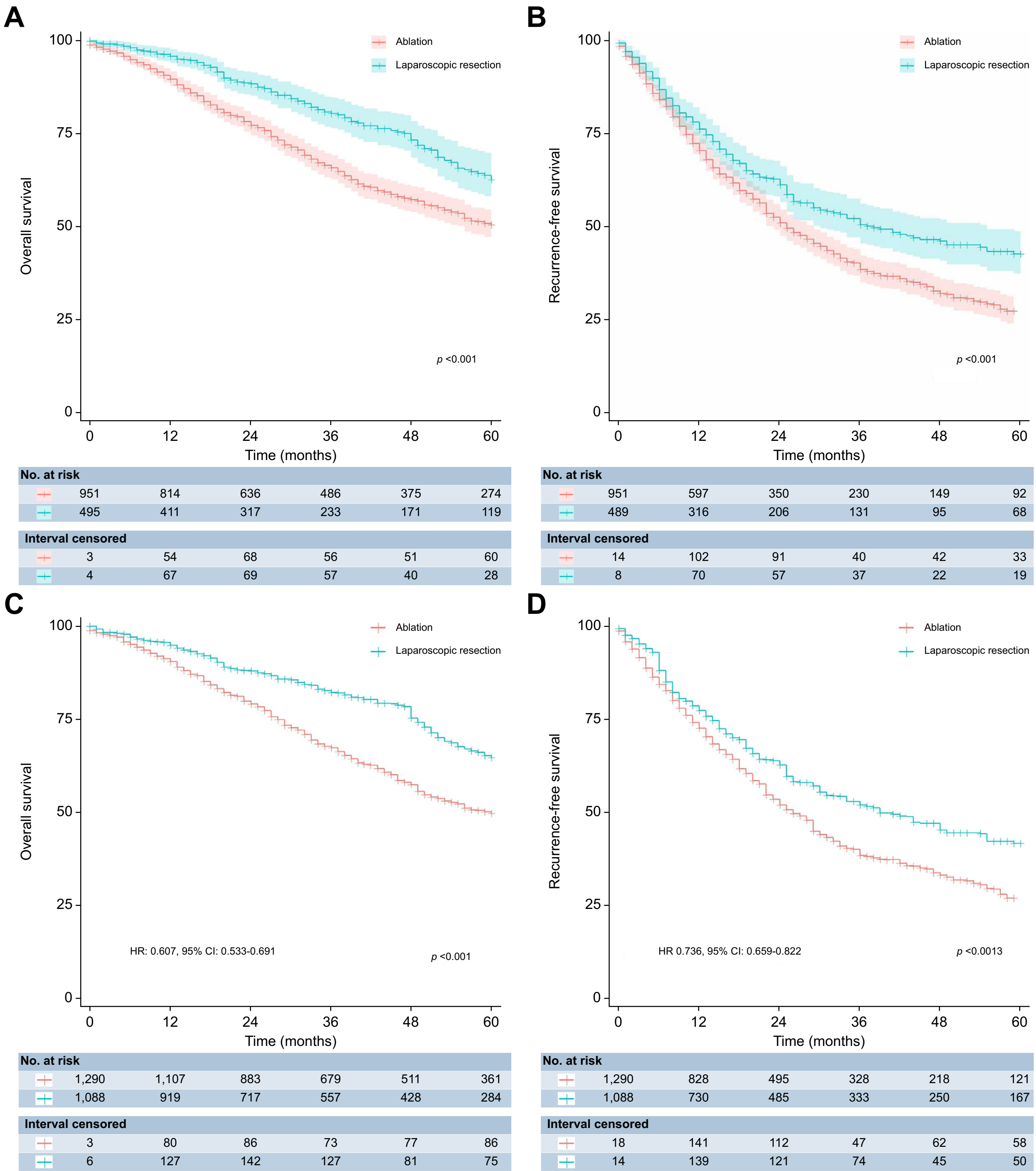
Median RFS was 26 months (95% CI 23–29) for ablation patients and 39 months (95% CI 30–55) for laparoscopic resection patients (HR 0.736, 95% CI 0.659–0.822, *p* = 0.0013) (Fig. 1D). At the multivariable analysis, being treated by laparoscopic resection (HR 0.757, 95% CI 0.62–0.91, *p* = 0.004) and presence of cirrhosis (HR 1.387, 95% CI 1.05–1.81, *p* = 0.017) were independently associated with the risk of recurrence (Table 3). The effect of the treatments was tested also in different subgroups (exploratory analysis), and the results are depicted in Fig. 3B. Briefly, laparoscopic resection was not inferior (HR 0.757, 95% CI 0.56–1.02) to ablation in determining the risk of recurrence for tumors ≤2 cm.

A sensitivity analysis was done by repeating the survival estimation after propensity score matching to confirm the stability of the IPTW results: with the same variables considered for the IPTW, 323 patients were correctly matched per each group. The effect of the matching has been depicted in Fig. S3. Median OS was 56 months (95% CI 50–66) for ablation and 87 months (95% CI 74–107) for laparoscopic resection. Median RFS were 24 months (95% CI 20–29) and 39 (95% CI 30–64) for ablation and laparoscopic resection groups, respectively. Survival curves were depicted in Fig. S4 (OS) and 5 (RFS).

Pattern of recurrence and following treatments

Considering the 'early' recurrence, after IPTW, patients who underwent ablation showed 6-, 12-, and 24-month early RFS of 84.7%, 72.8%, and 52.1% respectively, whereas for those who had a laparoscopic resection these figures increased to 87.9%, 77.2%, and 62.3%, respectively (HR 0.747, 95% CI 0.655–0.853, *p* = 0.011, Fig. 4).

An intrahepatic recurrence was observed in 485 (85.4%) and 178 (79.5%) patients in the ablation and laparoscopic resection



A

No. at risk	0	12	24	36	48	60
Ablation	951	814	636	486	375	274
Laparoscopic resection	495	411	317	233	171	119
Interval censored						
Ablation	3	54	68	56	51	60
Laparoscopic resection	4	67	69	57	40	28

B

No. at risk	0	12	24	36	48	60
Ablation	951	597	350	230	149	92
Laparoscopic resection	489	316	206	131	95	68
Interval censored						
Ablation	14	102	91	40	42	33
Laparoscopic resection	8	70	57	37	22	19

C

No. at risk	0	12	24	36	48	60
Ablation	1,290	1,107	883	679	511	361
Laparoscopic resection	1,088	919	717	557	428	284
Interval censored						
Ablation	3	80	86	73	77	86
Laparoscopic resection	6	127	142	127	81	75

D

No. at risk	0	12	24	36	48	60
Ablation	1,290	828	495	328	218	121
Laparoscopic resection	1,088	730	485	333	250	167
Interval censored						
Ablation	18	141	112	47	62	58
Laparoscopic resection	14	139	121	74	45	50

Fig. 1. Survival curves between patients treated by videolaparoscopic liver resection (laparoscopic resection group) or by thermoablation. Overall survival (A) before IPTW and (C) after IPTW. Recurrence-free survival (B) before IPTW and (D) after IPTW. Comparison among groups was made using the log-rank test before weighting and by double-robust univariate Cox regression after the weighting.

groups, respectively, and an extrahepatic spread was present in nine (1.6%) and 12 (5.4%) patients, respectively (p = 0.010). A bilobar intrahepatic recurrence was observed in 110 (19.4%) and 41 (18.3%) patients of the ablation and laparoscopic resection groups, respectively (p <0.001). The median number of recurrent nodules was 1 (IQR 1–2) in the ablation and 1 (IQR 1–3) in the laparoscopic resection groups (p = 0.004). The median size of the recurrent nodule was 2.0 cm (IQR 1.40–2.70)

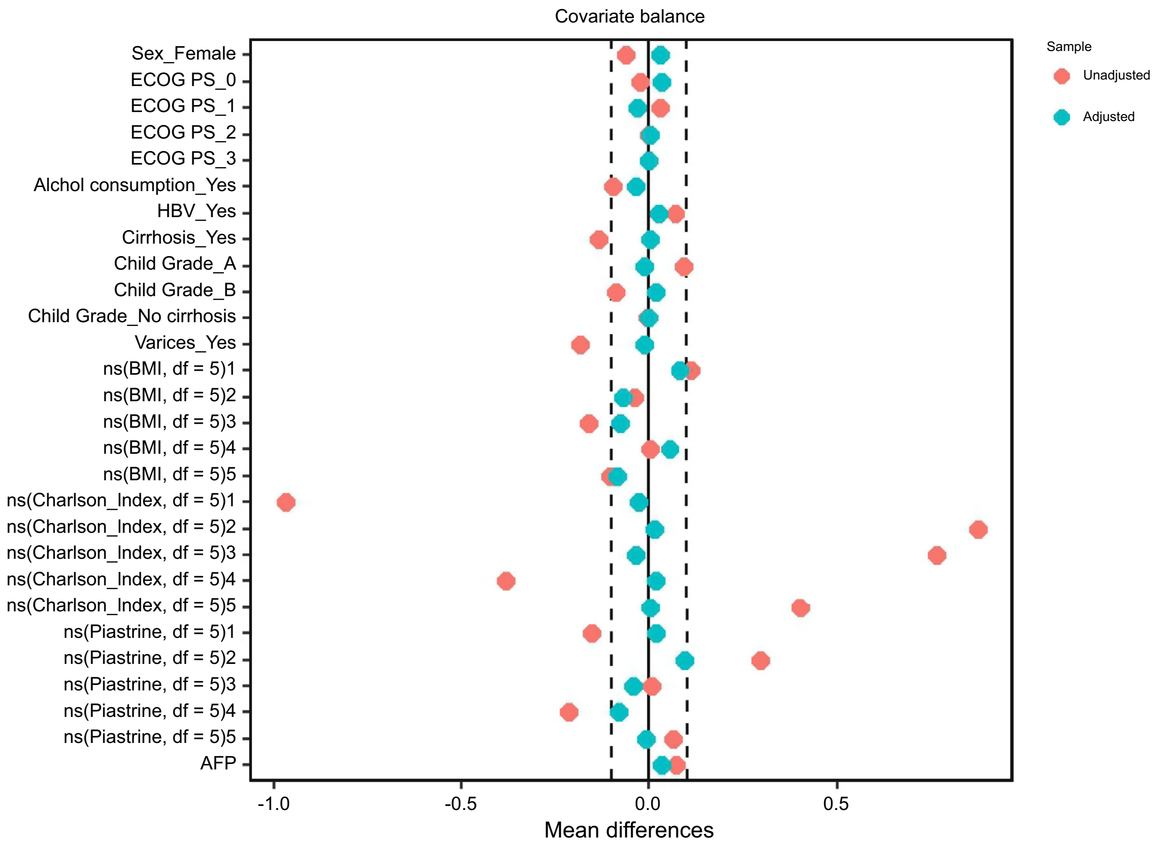


Fig. 2. 'Love' plot depicting the effect of the treatment weighting (IPTW) in terms of mean difference. The continuous black line represents the best possible weighting among variables, and the area among the two dashed lines represent an optimal balance obtained after IPTW. The red dots are the mean differences between groups for that variable before the weighting, and the blue dots are the mean difference after the weighting. 'Ns' before a continuous variable means that splines were applied to model that variable, and the relative total number of degrees of freedom (df) was indicated, with the reported results of each one of them. ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; IPTW, inverse probability of treatment weighting.

Table 2. Univariate and multivariate double robust Cox regression to predict the risk of overall mortality.

	Univariable				Multivariable			
Variable	**HR**	**95% CI –low**	**95% CI – up**	***p* value**	**HR**	**95% CI – low**	**95% CI – up**	***p* value**
Female (*vs.* male)	0.957	0.838	1.093	0.6844				
Laparoscopic resection (*vs.* ablation)	0.607	0.533	0.691	<0.001	0.714	0.571	0.893	0.0031
ECOG PS 1 (*vs.* 0)	1.127	0.921	1.380	0.4469	1.104	0.822	1.482	0.5121
ECOG PS 2 (*vs.* 0)	2.562	1.865	3.520	0.0003	2.108	1.306	3.403	0.0023
ECOG PS 3 (*vs.* 0)	4.947	1.853	13.208	0.0003	7.571	3.354	17.091	<0.001
Alcohol consumption (*vs.* not)	1.083	0.937	1.252	0.4775				
HBV+ (*vs.* neg)	1.037	0.866	1.243	0.7788				
HCV+ (*vs.* neg)	0.887	0.781	1.007	0.2249				
Cirrhosis (*vs.* not)	1.553	1.290	1.869	0.0057	1.275	0.911	1.784	0.1563
CPT class B (*vs.* A)	2.068	1.756	2.435	<0.001	1.729	1.280	2.334	0.0004
Varices (*vs.* not)	1.199	1.059	1.356	0.0674				
BMI	1.002	0.987	1.016	0.8884				
MELD (per unit)	1.019	1.000	1.038	0.1750				
N. nodules	0.844	0.615	1.158	0.4181				
Size (per cm)	1.075	0.981	1.178	0.3078				
Albumin (per unit)	0.757	0.680	0.843	0.0014	0.885	0.739	1.059	0.1816
INR (per unit)	1.000	0.996	1.004	<0.001	0.811	0.542	1.213	0.3083
AFP (per unit)	1.000	1.000	1.000	0.0118	1.000	1.000	1.000	0.7080
Age (per year)	1.009	1.003	1.015	0.0535	1.012	1.002	1.022	0.0172
Early recurrence (*vs.* not)	1.914	1.692	2.165	<0.001	1.781	1.465	2.165	<0.001
Charlson Comorbidity Index (per point)	1.071	1.049	1.094	0.0010	1.007	0.962	1.053	0.7718

Univariate and multivariate Cox regression was used to test the hypothesis. AFP alpha-fetoprotein; CPT, Child–Pugh–Turcotte score; ECOG PS Eastern Cooperative Oncologic Group - Performance Status; HR, hazard ratio; INR, International normalized ratio; low, 95% CI lower limit; MELD, model for end-stage liver disease; up, 95% CI upper limit; VLS, videolaparoscopy.

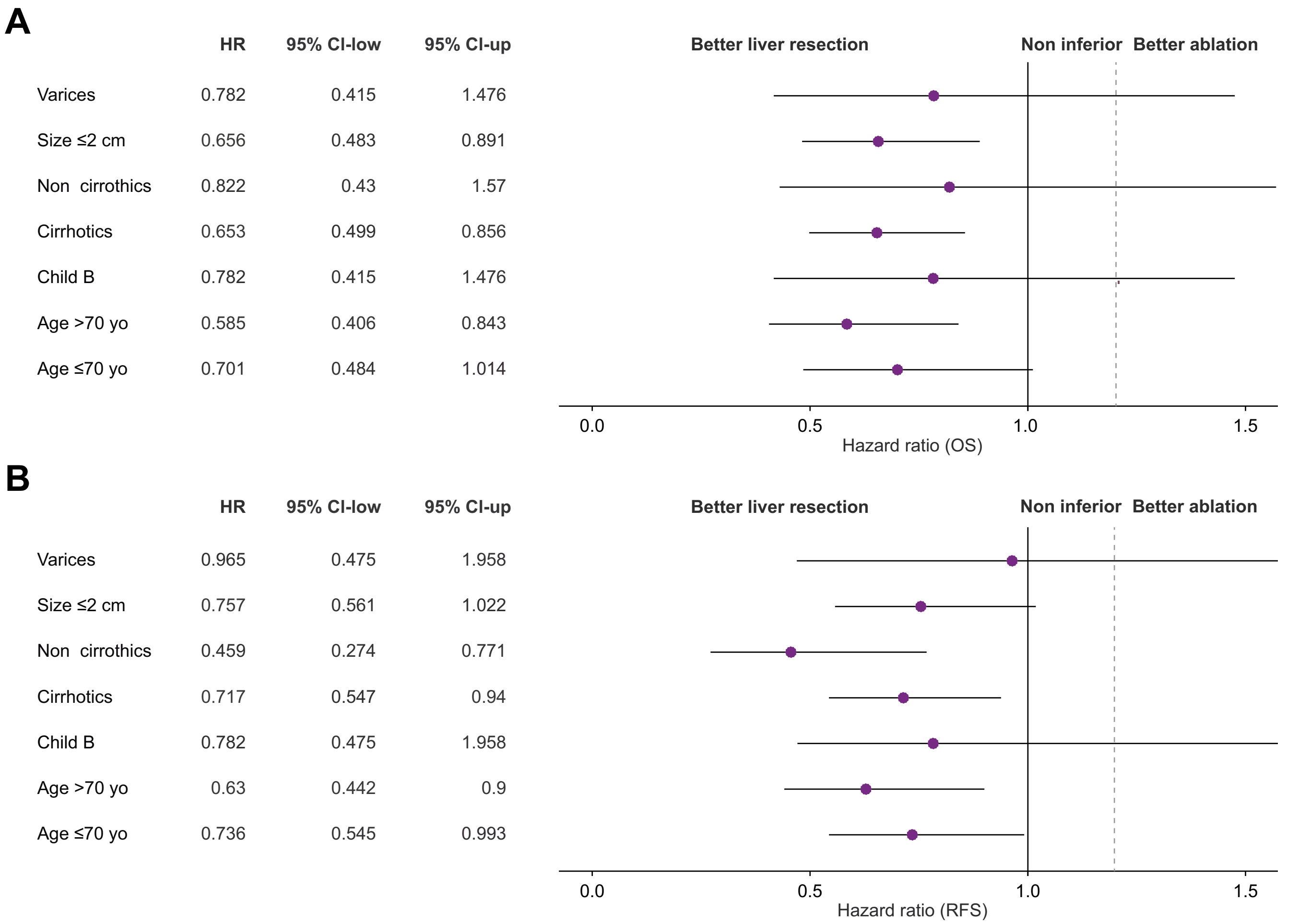
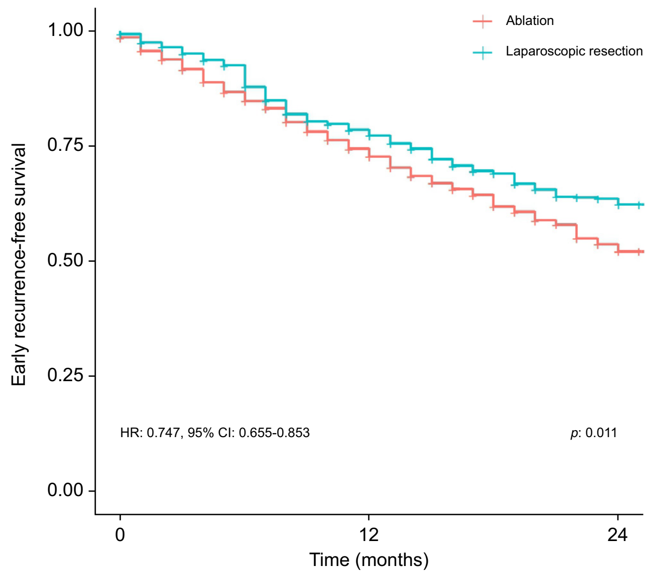


Fig. 3. Exploratory analysis: Forest plot reporting the effect of the treatment (after weighting) among different subgroups. The red dashed line represents the non-inferiority point adopted in this study. (A) The effect of the treatment on overall survival (OS). (B) The effect of the treatment on recurrence-free-survival. Comparison among groups was made by double-robust univariate Cox regression after the weighting.

Table 3. Univariate and multivariate double-robust Cox regression to estimate the risk of recurrence.

	Univariable				Multivariable			
Variable	**HR**	**95% CI – low**	**95% CI – up**	***p* value**	**HR**	**95% CI –low**	**95% CI – up**	***p* value**
Female (vs. male)	0.924	0.820	1.041	0.4183				
Laparoscopic resection (*vs.* ablation)	0.736	0.659	0.822	0.0013	0.757	0.624	0.919	0.0048
ECOG PS 1 (*vs.* 0)	0.947	0.792	1.132	0.7054				
ECOG PS 2 (*vs.* 0)	0.806	0.522	1.243	0.5705				
Alcohol consumption (*vs.* not)	1.214	1.073	1.373	0.0699				
HBV+ (*vs.* neg)	1.027	0.874	1.206	0.8443				
HCV+ (*vs.* neg)	1.053	0.939	1.179	0.5801				
Cirrhosis (*vs.* not)	1.475	1.261	1.725	0.0044	1.387	1.059	1.816	0.0176
CPT class B (*vs.* A)	1.124	0.941	1.343	0.4267				
Varices (*vs.* not)	1.233	1.105	1.376	0.0248	1.169	0.977	1.399	0.0885
BM	1.011	0.998	1.023	0.3040				
MELD (per unit)	0.985	0.969	1.001	0.2220				
N. nodules	0.792	0.585	1.071	0.1907				
Size (per cm)	1.119	1.029	1.216	0.0960				
Albumin (per unit)	0.949	0.884	1.018	0.2231				
INR (per unit)	1.000	1.000	1.000	0.4069				
AFP (per unit)	1.000	1.000	1.000	0.1614				
Age (per year)	0.994	0.989	0.999	0.1432				

Univariate and multivariate Cox regression was used to test the hypothesis. AFP, alpha-fetoprotein; CPT, Child–Pugh–Turcotte score; ECOG PS Eastern Cooperative Oncologic Group Performance Status; HR, hazard ratio; INR, International normalized ratio; low, 95% CI lower limit; MELD model for end stage liver disease; up, 95% CI upper limit; VLS, videolaparoscopy.



No. at risk			
Ablation	1,379	889	527
Laparoscopic resection	1,104	740	491

Fig. 4. Survival curve reporting the early-recurrence free survival between the two treatment groups. Comparison among groups was made using univariate double-robust Cox regression.

and 2.0 cm (1.35–2.85) in the ablation and laparoscopic resection groups, respectively (p = 0.932).

Five hundred and sixty-eight (58.6%) patients treated by ablation and 224 (45.2%) treated by laparoscopic resection had a disease recurrence. This was treated by liver transplant in 22 (3.9%) and 14 (6.2%) cases of ablation and laparoscopic resection groups, respectively; by hepatectomy in 45 (7.9%) and 33 (14.7%), respectively; by thermoablation in 197 (34.7%) and 36 (16.1%), respectively; by transarterial chemoembolization in 146 (25.7%) and 57 (25.4%), respectively; by systemic treatments in 24 (4.2%) and 25 (11.2%), respectively (p <0.001). Overall, a curative strategy for the recurrence was adopted in 264 (46.5%) patients of the ablation and 83 (37.1%) patients of the laparoscopic resection groups.

Discussion

Several previous reports have analyzed the outcomes of surgical resection and ablation, even though differences in indications for these treatments are well-recognized.[5,11] Typically, in the panorama of curative options, surgery is reserved for patients with larger tumors that are technically resectable, preserving enough liver remnant supporting hepatic functional reserve. Instead, patients with multiple comorbidities and/or a more deteriorated hepatic synthesis or particularly frail more often undergo ablation.[14,15]

To define the indication for these two treatments better, numerous observational studies and RCTs have been conducted.[6–10] However, the heterogeneity of the enrolled patients in terms of tumor burden, tumor location, or vascular contact, does not permit to achieve a solid evidence-based indication guiding the treatment decision in clinical practice. Among them, one RCT by Huang *et al.* [8] reported benefits in OS and RFS for surgery compared with ablation for HCC within Milan criteria. In the SURF trial,[10] surgery and ablation showed comparable oncologic results; however, patients with difficult tumor location were excluded, affecting a true comparison with surgery. Moreover, a recent meta-analysis suggests that RFA may offer better OS outcomes compared with minimally invasive surgery for single nodule presentations.[33]

This ambiguous scenario prompted us to conduct a study including a higher number of patients than the meta-analysis itself, on a real-life basis, in which the comparison between techniques was made in a well-defined oncologic setting – single and small (≤3 cm) HCC – where the uncertainty is maximal. It revealed a statistically significant, and clinically relevant, improvement in both OS and RFS when the tumor was treated with laparoscopic resection compared with ablation. In fact, in surgical patients the mortality risk was decreased by nearly 29%, and the risk of recurrence by nearly 25%, as confirmed in the weighted population, where the baseline's confounders were balanced. In 2013, Pompili *et al.*[34] reported comparable OS among surgery and ablation in another Italian national cohort, with the latter showing a slightly longer 4-year OS (66%) when compared with our result (near 60%). Although few of the present authors participated in that study, the present study derived from two large national real-world registers, with a larger number of participating centers and patients included a longer median follow-up. The study of Pompili *et al.* included referral centers; however, this study is based on national data, without restriction regarding the case volume. Reference centers may introduce selection bias by case selection, which do not reflect the broader patient population. Conversely, including a diverse range of centers, from small community hospitals to large academic institutions, provides a more representative sample of real-world clinical practice. Moreover, our study included patients regardless of their underlying liver function, whereas the previous study selected only Child–Pugh A patients. Nevertheless, in 2013 the number of laparoscopic cases was very small, and the relative non-inferiority of ablation over resection could be explained by the negative impact of open surgery in those with liver cirrhosis. This constatation led to develop the present study, to verify if laparoscopy could change the scenario, as effectively our results seem to demonstrate.

The favorable effect on RFS is somehow already accepted in the literature, as several authors[1] have reported an increased risk of recurrence and, particularly, of local recurrence with ablation, because this therapy focuses on eliminating target lesions, whereas surgical resection also removes a certain portion of liver tissue surrounding the tumor, thereby reducing the risk of leaving residual tumor tissue and satellites. In addition, it has been recently reported that biologic factors could be implied in the mechanism of recurrence after ablation, like the induction of epithelial-mesenchymal transition, promotion of angiogenesis, activation of autophagy, non-coding RNA changing, and modifications of the tumor environment.[35]

However, this drawback of ablation has been partially accepted because of the lower invasiveness and costs associated with an OS comparable with liver resection. The results of the present study disprove this position. In our cohort, patients submitted to ablation not only had a lower OS and an increased rate of overall recurrence, but also a higher risk of 'early' recurrence compared with surgical patients. Because early recurrence, particularly when it occurs near to the treated lesion, can be considered a postoperative growth of unremoved cancer tissue (failure of treatment), our results further support the reason previously discussed: an enucleo-ablation of the tumor is not enough to treat this disease radically.[15,36]

To overcome this risk, anatomic or sub-anatomic resections have been adopted as the standard treatments in most resected patients. In fact, the presence of segmental microvascular invasion (MVI) or satellitosis is high also in the case of single small HCC (in our cohort MVI = 27.4% and satellitosis = 8.8%), and an effective local control is not achievable without a proper removal of that area.[37] The 'early' recurrence was an independent predictor of OS too, regardless of the treatment utilized. This means that a technique that leads to an increased rate of early recurrence should be carefully proposed, when minimally invasive resection could be offered to patients. Although ablation is considered to be repeatable in case of local failure until a definitive local control, in our real-life study this happened only up to 34.7% of patients who experienced a recurrence after ablation. Although the reason for not repeating the ablation cannot be reported according to the data collected in the registers, this is a real-life snapshot of what happens. Even if multiple repeated ablations could be efficient, actually this was not the first strategy adopted in most patients. Because of this, submitting those patients to ablation significantly increases the oncologic patients' risk, without a certainty of being able to repeat ablation in case of relapse. Similar observations, particularly in case of ablation for tumors between 2 and 3 cm, were recently reported.[10,38]

The superiority of laparoscopic resection over ablation in terms of OS was confirmed also in subgroup analysis, particularly in the cohort of patients with a tumor size <2 cm, confirming the advantage of laparoscopic resection, when feasible, for any tumor characteristics. However, the exploratory nature of such analysis should be carefully evaluated in interpreting this result.

Our results came from a weighted analysis that took into account all the available confounders in determining the oncologic risk. The multivariable analysis indicates that the risk of recurrence, early recurrence, and OS was independently associated not only with the curative therapy used, but also with other well-known factors, such as age, presence of cirrhosis, its severity, and comorbidities. At baseline, patients undergoing ablation were more compromised, with significantly more deteriorated liver function, high rate of varices, and comorbidities. For frail patients, ablation should be theoretically preferred, because the perioperative risk of a liver resection could overcome the oncologic benefit. Nevertheless, Giuliante *et al.*[39] recently reported optimal short-term outcomes when a minimally invasive resection was adopted for small HCC, almost comparable to the ones obtained in the case of percutaneous ablation. However, other authors did not confirm this result,[33] and probably a randomized clinical trial could be the only way to clarify definitively if the laparoscopic approach is equivalent also in terms of perioperative risk. Our results should be interpreted in light of a therapeutic hierarchy strategy,[40] which postulates that the choice between resection or ablation is not dependent on the morphologic presentation (number, size, etc.) of the tumor, but should be guided by the technical feasibility and the patient risk evaluated by a multidisciplinary tumor board considering many clinical factors and patient opinion. Given that, after transplantation, liver resection is the best option, it should be preferred and, if the patient's risk is deemed to be high, ablation becomes the best choice, being able to ensure an acceptable (although inferior to surgery) survival.

Limitations of our study. First, the retrospective nature of the analysis poses a challenge regarding the comparison between the two treatments, partially mitigated by the weighting technique. Secondly, the choice between videolaparoscopy and ablation was not driven by a pre-defined algorithm, and the number of patients excluded from surgery by clinical or technical reasons could not be assessed. This could have revealed more consistent conclusions. Because of the oncologic nature of the two databases that provided the cases for the analysis, no comparison was possible to define the best treatment in terms of perioperative outcomes, such as rate of complications or length of stay. Moreover, RFA and MWA were considered together in the ablation group because they were recorded together in the ITA.LI.CA. register. Although these techniques showed comparable long-term results (even with different technical applications), treating them as a unique group could have driven bias, particularly in terms of local recurrence. This last information was not reported in the ITA.LI.CA. dataset, leading to the impossibility to estimate properly the risk of local recurrence under ablation approaches. This has been partially mitigated by adopting the parameter of early recurrence, which could be considered a sort of surrogate. Nevertheless, it is important to acknowledge that early recurrence and local tumor progression are distinct oncologic events. Local tumor progression refers specifically to residual or regrowth of the tumor at the original ablation site, often as a result of incomplete ablation, whereas early recurrence encompasses both local and distant recurrences and may be influenced by biological tumor aggressiveness rather than solely reflecting the efficacy of local treatment. Although the diagnosis was histologically proven for the surgical patients, in the ablation group the diagnosis was confirmed by the radiologic interpretation of the preoperative imaging made by dedicated radiologists. However, the study did not provide imaging centralization for re-evaluation. Finally, the unretrievable data on tumor locations (superficial *vs.* deep located nodules, vascular contacts etc.) could introduce bias in the comparison among the two treatments, probably reducing the performance of the ablation group. To conclude, our findings strongly advocate for laparoscopic resection over ablation in patients with single HCC ≤3 cm in size, and support the importance of considering minimally invasive resection whenever clinically feasible, addressing most critical patients to referral centers.

Affiliations

[1]*Hepatobiliary Surgery Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy;* [2]*IRCAD, Research Institute Against Cancer of the Digestive System, Strasbourg, France;* [3]*Department of Medicine and Surgery, Infectious Diseases and Hepatology Unit, University of Parma and Azienda Ospedaliero-Universitaria of Parma, Parma, Italy;* [4]*Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and C.R.C. "A.M. & A. Migliavacca Center for Liver Disease", Milan, Italy;* [5]*Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padova, Second General Surgical Unit, Padova Teaching Hospital, Padua, Italy;* [6]*Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), Gastroenterology & Hepatology Unit, University of Palermo, Palermo, Italy;* [7]*General*

Surgery and Abdominal Organ Transplantation, ASST Grande Ospedale Metropolitano Milano Niguarda; School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [8]Hepatobiliary Surgery Division, "Vita e Salute" University, Ospedale San Raffaele IRCCS, Milan, Italy; [9]Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy; [10]Department of Medicine, Surgery and Pharmacy. Azienda Ospedaliero-Universitaria of Sassari, Sassari, Italy; [11]Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padua, Padua, Italy; [12]Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa, Pisa, Italy; [13]Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina, Messina, Italy; [14]Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy; [15]Department of Experimental and Clinical Medicine, Internal Medicine and Hepatology Unit, University of Florence, Florence, Italy; [16]Medicine Unit, Bolognini Hospital, Seriate, Italy; [17]Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [18]Unit of Semeiotics, Liver and Alcohol Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [19]Department of Clinical Medicine and Surgery, Diseases of the Liver and Biliary System Unit, University of Naples "Federico II", Naples, Italy; [20]Gastroenterology Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Italy; [21]Department of General and Oncological Surgery, Mauriziano Hospital "Umberto I", Turin, Italy; [22]Department of General and Specialized Surgery, Division of General Surgery, Parma University Hospital, Parma, Italy; [23]Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Naples "Federico II", Naples, Italy; [24]Hepato-biliary Surgery and Transplant Unit, Policlinico Sant'Orsola IRCCS, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [25]Gastroenterology Unit, Bolzano Regional Hospital, Bolzano, Italy; [26]Liver Unit, CEMAD – Centro Malattie Dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Università Cattolica Del Sacro Cuore, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; [27]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; [28]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [29]School of Medicine and Surgery, University of Milano-Bicocca; IRCCS San Gerardo Dei Tintori Hospital, Monza, Italy; [30]Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy; [31]Division of Gastroenterology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [32]Division of Hepatobiliarypancreatic Unit, IRCCS - Regina Elena National Cancer Institute, Rome, Italy; [33]Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy; [34]Division of Hepato-biliary-pancreatic, Minimally Invasive and Robotic Surgery, and Transplantation Service Federico II University Hospital, Naples, Italy; [35]HPB Surgical Unit, San Paolo Hospital, Savona, Italy; [36]Department of General Surgery, Ospedale Carlo Poma, Mantua, Italy; [37]Department of Surgery, L. Sacco Hospital, Milan, Italy; [38]Division of Internal Medicine, Neurovascular and Hepatometabolic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [39]HPB Surgery and Transplantation Unit, Department of Clinical and Experimental Medicine, Polytechnic University of Marche, Ancona, Italy; [40]Department of General Surgery, Poliambulanza Foundation Hospital, Brescia, Italy; [41]Division of General Surgery, Department of Medical and Surgical Sciences, ASUGI, Trieste, Italy; [42]Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona, Italy; [43]Department of Hepato-Pancreatc-Biliary Surgery, "F. Miulli" General Regional Hospital, Acquaviva Delle Fonti, Bari, Italy; Department of Medicine and Surgery, LUM University, Casamassima, Bari, Italy; [44]Alma Mater Studiorum, University of Bologna, AOU Sant'Orsola Malpighi, IRCCS at Maggiore Hospital, Bologna, Italy; [45]Department of Surgical, Oncological and Gastroenterological Science (DISCOG), University of Padua, Hepatobiliary and Pancreatic Surgery Unit - Treviso Hospital, Italy; [46]Department of Hepatobiliary and General Surgery, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [47]General Surgery and Organ Transplantation Unit, Sapienza University of Rome, Umberto I Polyclinic of Rome, Rome, Italy; [48]Department of General and Pediatric Surgery, Bolzano Central Hospital, Bolzano, Italy; [49]HepatoBiliaryPancreatic Unit - AOU Careggi - University of Florence, Florence, Italy; [50]Center of Biostatistics for Clinical Epidemiology, School of Medicine and Surgery, University of Milan - Bicocca, Monza, Italy

Abbreviations

AFP, alpha-fetoprotein; ATE, average treatment effect; CCI, Charlson Comorbidity Index; CPT, Child–Pugh–Turcotte; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; HCC, Hepatocellular carcinoma; HR, hazard ratio; INR, International normalized ratio; IPTW, inverse probability of treatment weighting; LTP, local tumor progression; MAR, missing at random; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; MVI, microvascular invasion; MWA, microwave ablation; OS, overall survival; PS, propensity score; RCT, randomized clinical trial; RFA, radiofrequency ablation; RFS, recurrence-free survival; VLS, videolaparoscopy.

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: FG. Methodology: SF, FTrevisani. Formal analysis: SF, DPB. Investigation: FRazionale, GM, AO, GA, PR, CCammà, CCelsa, PG, CMG, GR, MVG, RC, AG, MSalvato, RDC, FRatti, LN, AB, FC, LI, MF, NR, FF, FB, GPalano, MPK, FO, GRicco, VR, RF, CP, GRaimondo, VL, GPelecca, TLC, LR, SG, MR, VA, AG, FTovoli, BernardoS, MB, LL, BenedettaS, MGuarino, VC, AI, FMarchetti, NR, MGiuffrida, PC, ARocco, LM, NdM, FRP, AP, GPieri, CCiulli, MScotti; IM, AP, VDP, EMC, AFacciorusso, RP, AFranceschi, LM, DC, CScorzoni, GS, AC, PPelizzo, FProcopio, ZLL, FN. Writing – original draft: SF, SG, ASangiovanni, AV, GC, AL, FC, ASaccomandi, MA, EP, MRB, MSF, CG, CC, FM, MDM, MM, VS, MCapasso, AMasotto, AFontana, MI, AR, MSerenari, AMega, AG, MCPT, MGarancini, SC, ED, PPerri, RS, MGiglio, CF, MDA, AT, DM, DN, GZimmitti, PG, LS, MConticchio, MZ, MRomano, FMilana, QLai, SP. Writing – review and editing: FG, AFrena, MRossi, GT, GZanus, EJ, RM, GS-B, PT, MAH, MV, MCrespi, LB, GGriseri, RIT, GLG, FAzzaroli, ARuzzenente, FR, EGG, MCescon, GN, RDV, AFerrero, FMorisco, FP, GGhittoni, CSaitta, FPelizzaro, GV, FGF, LA, LDC, UC, EB, DB, FArdito, FTrevisani. Supervision: SF, FTrevisani, FG.

Data availability statement

Data are available upon reasonable request to the corresponding author.

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Supplementary data

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Author names in bold designate shared co-first authorship

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Appendix 1. HE.RC.O.LE.S and ITA.LI.CA Contributors

Francesco Razionale[1], Gabriele Missale[2], Andrea Olivani[2], Gloria Allegrini[3], Pierluigi Romano[4], Calogero Cammà[5], Ciro Celsa[5], Paolo Giuffrida[5], Carmelo Marco Giacchetto[5], Gabriele Rancatore[5], Maria Vittoria Grassini[6], Roberta Ciccia[5], Alessandro Grova[5], Mauro Salvato[5], Riccardo De Carlis[6], Francesca Ratti[7], Lucia Napoli[8], Alberto Borghi[8], Fabio Conti[8], Luca Ielasi[8], Marco Ferronato[8], Nicola Reggidori[8], Fabio Farinati[9], Federica Bertellini[9], Giorgio Palano[9], Maria Piera Kitenge[9], Filippo Oliveri[10], Gabriele Ricco[10], Veronica Romagnoli[10], Roberto Filomia[11], Concetta Pitrone[11], Giovanni Raimondo[11], Valentina Lauria[12], Giorgio Pelecca[12], Tancredi Li Cavoli[13], Lucia Ragozzino[13], Stefano Gitto[13], Martina Rosi[13], Valentina Adotti[13], Alessandro Granito[14], Francesco Tovoli[14], Bernardo Stefanini[14], Maurizio Biselli[15], Lorenzo Lani[15], Benedetta Stefanini[15], Maria Guarino[16], Valentina Cossiga[16], Alessandro Inno[17], Fabiana Marchetti[17], Nadia Russolillo[18], Mario Giuffrida[19], Pietro Coccoli[20], Alba Rocco[20], Luca Marzi[21], Nicoletta de Matthaeis[22], Francesca Romana Ponziani[22], Andrea Pasta[23,24], Giulia Pieri[23,24], Cristina Ciulli[25], Mauro Scotti[25], Ivan Marchitelli[26], Alberto Porro[27], Valerio De Peppo[28], Ester Marina Cela[29], Antonio Facciorusso[29], Renato Patrone[30], Angelo Franceschi[31], Laura Marinelli[32], Davide Cosola[33], Chiara Scorzoni[34], Giulia Scandali[34], Annachiara Casella[35], Patrizia Pelizzo[36], Fabio Procopio[37], Zoe Larghi Laurerio[38], Francesca Notte[39].

[1]Hepatobiliary Surgery Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy; [2]Department of Medicine and Surgery, Infectious Diseases and Hepatology Unit, University of Parma and Azienda Ospedaliero-Universitaria of Parma, Parma, Italy; [3]Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and C.R.C. "A.M. & A. Migliavacca Center for Liver Disease", Milan, Italy; [4]Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padova, Second General Surgical Unit, Padova Teaching Hospital, Padua, Italy; [5]Section of Gastroenterology and Hepatology. Department of Health Promotion, Mother & Child Care, Internal Medicine & Medical Specialties (PROMISE), Gastroenterology & Hepatology Unit, University of Palermo, Palermo, Italy; [6]General Surgery and Abdominal Organ Transplantation, ASST Grande Ospedale Metropolitano Milano Niguarda; School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [7]Hepatobiliary Surgery Division, "Vita e Salute" University, Ospedale San Raffaele IRCCS, Milan, Italy; [8]Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy; [9]Department of Surgery, Oncology and Gastroenterology, Gastroenterology Unit, University of Padua, Padua, Italy; [10]Department of Clinical and Experimental Medicine, Hepatology and Liver Physiopathology Laboratory, University Hospital of Pisa, Pisa, Italy; [11]Department of Clinical and Experimental Medicine, Clinical and Molecular Hepatology Unit, University of Messina, Messina, Italy; [12]Gastroenterology Unit, Belcolle Hospital, Viterbo, Italy; [13]Department of Experimental and Clinical Medicine, Internal Medicine and Hepatology Unit, University of Florence, Florence, Italy;[14] Medicine Unit, Bolognini Hospital, Seriate, Italy; [15]Unit of Semeiotics, Liver and Alcohol Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [16]Department of Clinical Medicine and Surgery, Diseases of the Liver and Biliary System Unit, University of Naples "Federico II", Naples, Italy; [17]Gastroenterology Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Italy; [18]Department of General and Oncological Surgery, Mauriziano Hospital "Umberto I", Turin, Italy; [19]Department of General and Specialized Surgery, Division of General Surgery, Parma University Hospital, Parma, Italy; [20]Department of Clinical Medicine and Surgery, Hepato-Gastroenterology Unit, University of Naples "Federico II", Naples, Italy; [21]Gastroenterology Unit, Bolzano Regional Hospital, Bolzano, Italy; [22]Liver Unit, CEMAD – Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy; [23]Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy; [24]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [25]School of Medicine and Surgery, University of Milano-Bicocca; IRCCS San Gerardo dei Tintori Hospital, Monza, Italy; [26]Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy; [27]Division of Gastroenterology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [28]Division of Hepatobiliarypancreatic Unit, IRCCS - Regina Elena National Cancer Institute, Rome, Italy; [29]Gastroenterology and Digestive Endoscopy Unit, Foggia University Hospital, Foggia, Italy; [30]Division of Hepato-biliary-pancreatic, Minimally Invasive and Robotic surgery, and Transplantation Service Federico II University Hospital, Naples, Italy; [31]HPB Surgical Unit, San Paolo Hospital, Savona, Italy; [32]HPB Surgery and Transplantation Unit, Department of Clinical and Experimental Medicine, Polytechnic University of Marche, Ancona, Italy; [33]Division of General Surgery, Department of Medical and Surgical Sciences, ASUGI, Trieste, Italy; [34]Liver Injury and Transplant Unit, Polytechnic University of Marche, Ancona, Italy; [35]Department of Hepato-Pancreatc-Biliary Surgery, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti, Bari; Department of Medicine and Surgery, LUM University, Casamassima, Bari, Italy; [36]Department of Surgical, Oncological and Gastroenterological Science (DISCOG), University of Padua, Hepatobiliary and Pancreatic Surgery Unit - Treviso Hospital, Italy; [37]Department of Hepatobiliary and General Surgery, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [38]General Surgery and Organ Transplantation Unit, Sapienza University of Rome, Umberto I Polyclinic of Rome, Rome, Italy; [39]Department of General and Pediatric Surgery, Bolzano Central Hospital, Bolzano, Italy.